What factors influence socioeconomic inequalities in colorectal cancer survival?

Lorraine Gillian Shack

This Thesis is submitted for the Degree of Doctor of Philosophy

Supervisors:
Dr. Bernard Rachet and Professor Michel Coleman

Non-communicable Disease Epidemiology Unit
Department of Epidemiology and Population Health
London School of Hygiene and Tropical Medicine

Declaration of own work

I have read and understood the School's definition of plagiarism and cheating given in the Research Degrees Handbook. I declare that this thesis is my own work, and that I have acknowledged all results and quotations from the published or unpublished work of other people.

Signed,

Lorraine G. Shack Date: 18th March, 2009

Abstract

Colorectal cancer treatment and survival is improving, but deprived patients continue to receive less than optimal treatment and have lower survival than affluent patients. Population-based data on all patients diagnosed with colorectal cancer in the North West (n=29,563) was linked to hospital admissions (n=6 million) to provide complete information on cancer diagnosis, treatment and other comorbid conditions. In order to handle incomplete data, particularly for stage at diagnosis, multiple imputation was used.

Socioeconomic inequalities in survival have been attributed to deprived patients presenting at a more advanced stage or with more comorbid conditions than affluent. In this research there were no socioeconomic variations in stage at diagnosis but deprived patients did have higher levels of comorbidity, which may limit their treatment options. Even after taking clinical and demographic factors into account, deprived patients still received less adjuvant therapy, surgery from high-volume surgeons and treatment in compliance with clinical guidance

Socioeconomic inequalities in survival were substantial at one year after diagnosis and could not be explained by clinical or demographic factors, such as stage and comorbidity. Even when deprived patients did receive the same treatment regime or surgery from a higher-volume hospital or higher-volume surgeon survival was lower. The factors contributing to these inequalities in treatment are complex including physical, social, lifestyle and clinical domains. Ensuring equal access to services and equal improvement in survival across all social groups will be a continuing challenge for the NHS. Ultimately, a universal health-care system may not be able to achieve equal survival, because of external factors that cannot be controlled, but ensuring equitable access would be expected to greatly reduce the inequalities in colorectal cancer survival.

Acknowledgements

A big thank you to both Bernard Rachet and Michel Coleman, my supervisors, for their support, direction and enthusiasm in my work through the three years. In particular Bernard for his brilliant statistical advice and Michel for keeping me to timelines!

Also a big thank you to Lyn Williams for all her valuable advice and comments.

Many thanks to Natalie Friend-du Preez for her practical advice and encouragement. Thank you also to my colleagues at NWCIS, and everyone else involved in data collection and quality assurance, thus making this work possible. I would particularly like to thank Kath Chester, Sharon Bishop, Becky Taylor, Lesley Wilcox and Doreen Hurst for their help in quality assurance of data, IT support and administrative support.

Special thanks to all those (you know who you are!) who made me work when I did not want to and take those much needed breaks.

The research undertaken for this PhD was made possible through the support of NWCIS, as part of their research programme.

The aims of this thesis

The aim of this thesis was to identify factors that influence socioeconomic differences in survival in patients diagnosed with colorectal cancer in the North West Region of England 1997-2004. These assessments can then be used to inform public health policy and other initiatives targeted to decrease inequalities in survival in the UK.

The underlying purpose of this thesis was to investigate the use of routine data sources to evaluate prognosis and patterns in colorectal cancer treatment, comorbid conditions, and stage and the impact on survival. Equity in the provision and quality of treatment was assessed with the subsequent impact on inequalities in survival evaluated.

Secondary aims were to assess and develop the methodology for i) linking cancer registry data to administrative datasets, ii) estimating comorbid conditions and iii) multiple imputation of missing data for use in relative survival analysis.

Introduction

Health inequalities have long been documented between socioeconomic groups and these inequalities have been seen in UK cancer patients with regard to incidence, mortality, survival[1-3] and treatment.[4,5] The inequalities have frequently been attributed to deprived patients presenting at a later clinical stage. However, even after adjustment for clinical stage at diagnosis, deprivation differences in survival persist.[6,7]

Treatment is a major factor influencing outcomes at any given stage but clinical treatment regimes vary by prognostic factors, including age, stage, comorbidity and anatomic location. Some studies have found that treatment provision also varies by socioeconomic factors.[8-10] National guidelines set out minimum standards for treatment. These guidelines are applicable to all patients regardless of their socioeconomic status, but new treatment regimes may nevertheless be implemented more quickly in some areas than others, thereby contributing to socioeconomic and geographic disparities in outcome. More controversially, implementation of new treatment regimes could be made available more rapidly for patients in some socioeconomic groups than others, independent of where they live. This could lead to persistence of socioeconomic disparities in outcome. After receiving treatment, some studies report the outcomes to be similar among all socioeconomic groups[11] while others suggest it persists.[12] Research on the patterns of treatment given to cancer patients, both as a function of their socioeconomic status and in relation to the implementation of contemporary clinical practice guidelines, should help elucidate the impact of differential access to optimal treatment on socioeconomic differences in cancer survival.

Summary of objectives

- To describe and identify factors, including age, socioeconomic status and stage at diagnosis, that influence colorectal cancer outcomes, type and quality of treatment, and to set these results in the context of the current literature.

- To identify the factors contributing to differences in survival between socioeconomic groups in order to inform policy and future interventions.

- To evaluate differences in treatment type, quality and provision by socioeconomic group and other demographic and clinical factors, and the extent to which these influence inequalities in survival.

Table of Contents

List of Tables

List of Figures

Chapter 1

Introduction

Cancer

Cancer is a term used to describe neoplasms, or new growth, resulting from uncontrolled proliferation of cells. "Cancer" is a term widely used to describe all neoplastic growths, however many different diseases are defined as cancer, each with different presentation, prognosis and treatment. Cancers develop due to genetic damage, which may happen randomly or as a result of exposure to carcinogens. Once a tumour has developed it will continue to grow even if carcinogens are removed. Tumours can be benign, *in situ*, or invasive, depending on their cell growth and behaviour.

Benign tumour cells have mutations but appear very similar to the cells from which they originated. The tumour itself is generally encapsulated and can be removed relatively easily. Benign tumours are rarely fatal except for those arising within the central nervous system, which can cause fatal compressions of the brain.

In situ tumours have malignant cells but are confined to the site of origin without invading the organ. The localised tumour can usually be removed easily without the need for further treatment. However, if left untreated an *in situ* tumour will invade the local organ and become an invasive tumour. *In situ* tumours are pre-invasive tumours with malignant cells present in the epithelium but there is no invasion beyond the basal lamina.

Invasive malignant tumours will infiltrate adjacent tissues to gain access to further blood supplies to aid growth. If left untreated they will break away and spread through out the body, known as *metastasis*, ultimately leading to death.

Colorectal tumours

Tumours of the colon and rectum can be benign, *in situ* or invasive. Benign tumours, also known as adenomas or polyps, develop into malignant adenocarcinomas at a slow rate with many polyps not progressing during the patient's life-time.[13-15] Adenomas are thought to occur due to mutations in the mucosal epithelium cells which regulated stem cell renewal, proliferation and differentiation.[16]

Adenocarcinomas develop from adenoma polyps which proliferate from glandular cells and are the most common type of colorectal cancer accounting for 90% to 95%.[17] There are a number of other types of tumour defined by their histology including adenosquamous cell and neuroendocrine but these are much rarer with each accounting for less than 0.5% of all colorectal cancers. Approximately 4% of patients have more than one primary colorectal cancer tumour diagnosed.

Polyps and colorectal cancer tumours are slow-growing which provides the possibility of early identification and removal.[13,17] Polyps are asymptomatic; they tend to be detected either incidentally or at screening.

Symptoms of colorectal cancer can be non-specific and may include rectal bleeding, weight loss, abdominal pain, anaemia, diarrhoea, constipation or change in bowel habits.[17-19] Many patients are asymptomatic until late in the disease and therefore may present at a late stage.[13] However, in a study in France most patients were diagnosed after presenting with symptoms (78%) with a small minority (6%) diagnosed incidentally.[20] A significant minority (14%) presented as an emergency with an obstructed or perforated bowel.[20] In the Merseyside and Cheshire region, within the North West of England, 73% of colorectal patients presented with symptoms, but it was not possible to determine whether presentation was as an emergency or non-emergency.[21] Only 3% of patients were diagnosed incidentally. Patients who present with colorectal cancer as an emergency and require urgent surgery have higher rates of complication, re-operation, anastomotic leakage and mortality.[22]

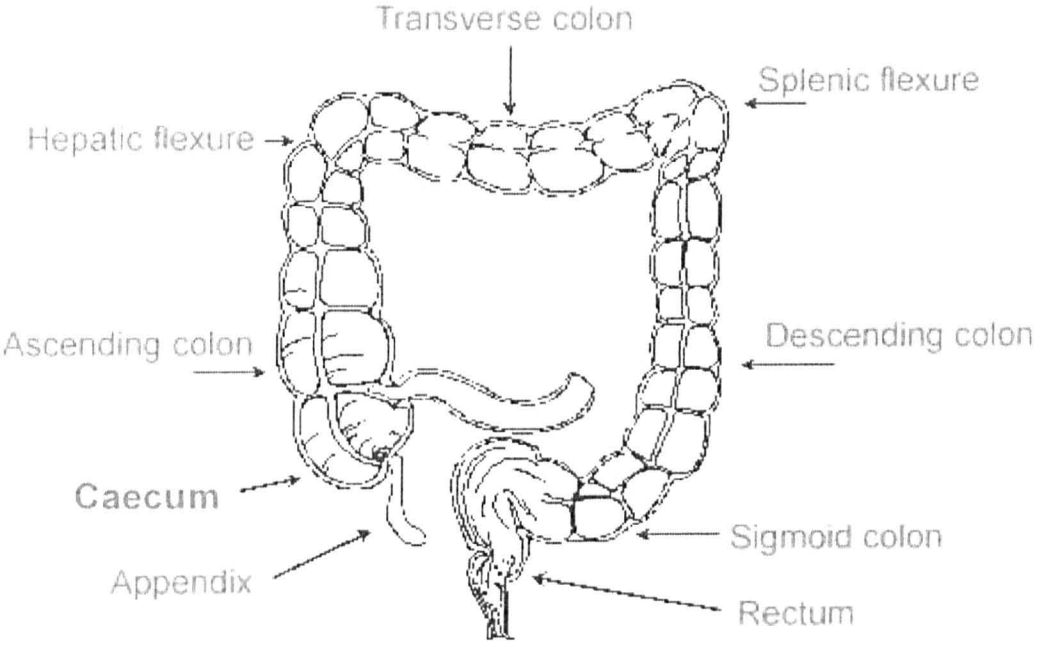
Sites

Colorectal cancer includes cancers of both the colon and rectum. Anal cancer (ICD-10 C21) is rare and is not normally included in analysis of colorectal cancer. Colon cancers of the right side, including cancers of the caecum, ascending colon, hepatic flexure and

transverse colon have been increasing in relative frequency over time in England and Wales,[23] and the USA.[16] A higher proportion of sigmoid cancers are found in countries with high colon cancer incidence,[16] such as the UK.

Colorectal cancer sites are unevenly distributed along the colorectum with the majority being diagnosed in the rectum (29%) and sigmoid colon (18%) (Figure 1.1).[24,25] The tumour sub-site could not be determined or were unspecified in 15% of colorectal cancers diagnosed during 1997-2000 in England.[24] In some patients, even after surgery, the primary site of origin cannot be determined because the tumour occured on the border of two sub-sites (overlapping).

Figure 1.1: Anatomic sites of the Colon and Rectum



Source: SEER. Anatomy of Colon and Rectum, 2006[26]

Colorectal cancer is more common in men than women.[16,23,27] Older men (over 65) are more likely to have left-sided tumours and younger women (under 65 years of age) are more likely to have right-sided colon tumours (excluding rectum).[16]

Tumour grade

Tumour grade describes the histologic similarity of the tumour cells to their tissue of origin. Tumours that are similar to the original tissue are moderately differentiated or low-grade, whereas tumours that are dissimilar to the tissue they developed from are poorly or undifferentiated and are high-grade.[28,29] High-grade tumours are generally

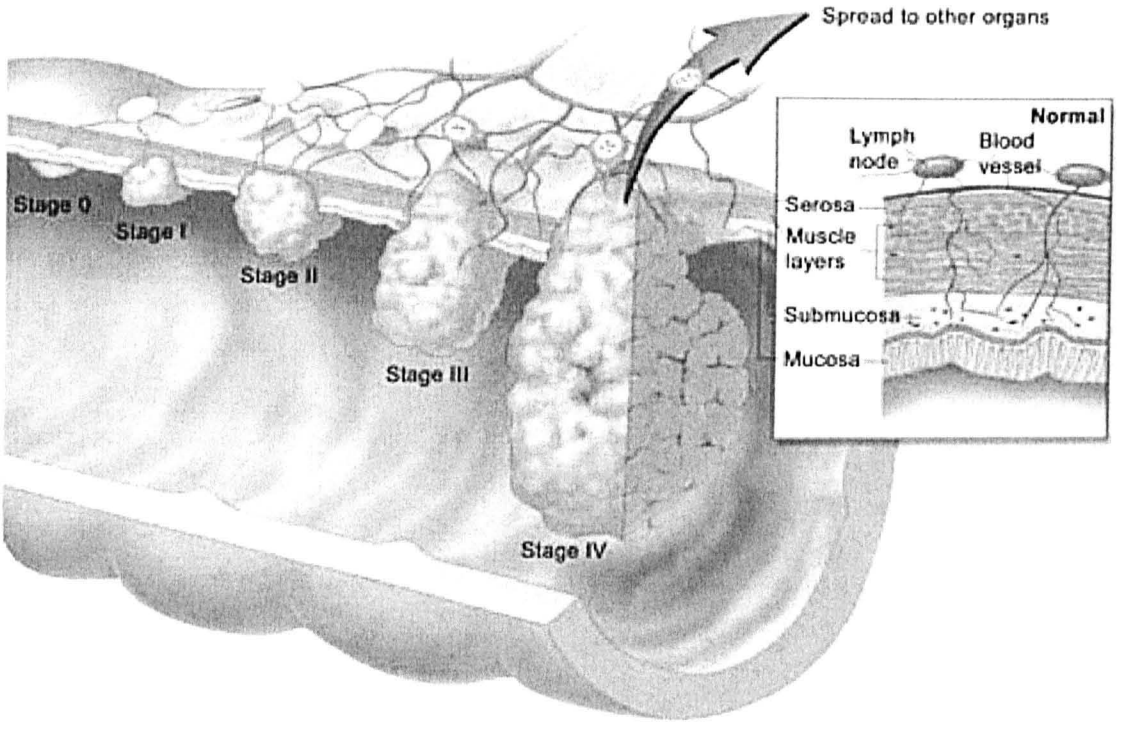
aggressive and have a poor prognosis. Colorectal cancer tumours are graded under the histopathological grading scheme which applies to all digestive system tumours, with tumours given a grade from I to IV. Grade I tumours have less than 25% of the cells undifferentiated with the proportion increasing until grade IV with over 75% of the cells undifferentiated. Grade is assigned on the basis of the tumour pathology and is subject to variation due to the subjective nature of classification and the variability within individual tumours.

Tumour stage

Stage is a measure of the extent of disease at diagnosis and is strongly correlated with a patients prognosis. Three staging systems are used for colorectal cancer: Dukes',[30] TNM[29] and contemporary versions of Dukes' including Astler-Coller.[31] The TNM staging system is also consistent with the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) systems. TNM and Dukes' are the most widely used systems but it is possible to convert from one system to another to produce comparable stage. Stage can be determined for all malignant tumours with benign or *in situ* tumours as stage 0.

TNM and Dukes' stage is determined by the extent of spread through the layers that form the wall of the colorectum (T), extent of lymphatic involvement as determined by positive lymph nodes (N) and spread or metastasis (M). Malignant tumours are staged from I to IV with patients in stage IV having metastatic disease (Figure 1.2).

Figure 1.2: Colorectal tumour stage



Source: University of Pittsburgh Cancer Centers, 2006[32]

Complete staging can only be done through post-operative pathology, however stage can be estimated pre-operatively through clinical symptoms and computed tomography and magnetic resonance imaging. In some cases, imaging can estimate tumour size accurately and positive lymph nodes.

Risk factors for colorectal cancer

Overview

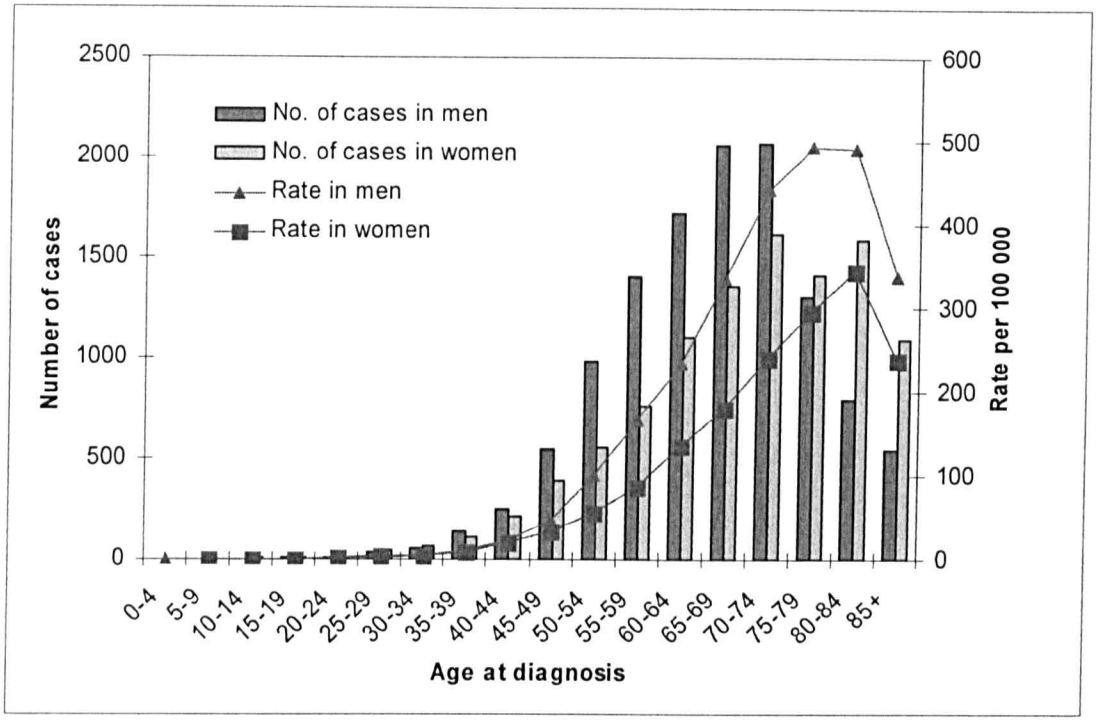
The majority of colorectal cancers are caused by environmental and lifestyle factors although hereditary or inflammatory diseases cause about 10%.[33] Colorectal cancer is a multi-factorial disease with increased risk associated with lifestyle choices including red meat consumption,[33] obesity,[34,35] lack of physical activity[34,35] and alcohol.[36] As with most cancers, risk increases with age and incidence is a slightly higher in men.

World-wide, colorectal cancer is more common in westernised countries where individuals have a high-risk lifestyle compared to non-westernised countries.[16,37] Migrant studies have found the risk of colorectal cancer to be similar to the general population in families that have immigrated within 1 or 2 generations, thereby reinforcing the importance of lifestyle characteristics on risk.[16,37,38] It is estimated that environmental factors account for over 70% of all colorectal cancers.[37,39]

Age

Colorectal cancer rarely occurs in individuals under 40 years of age but incidence and mortality rates increase consistently above age 40 (Figure 1.3) with the most common age at diagnosis being between 70 and 79. Incidence rates increase until the 80-84 age group and dropped after 85 years. Colorectal cancer death rates peak in the 75-79 age group and consistently increase with age. Men had consistently higher age-specific incidence and mortality rates.

Figure 1.3: Colorectal cancer incidence, North West England by age at diagnosis, 1999-2003



Source: Merseyside and Cheshire Cancer Registry, 2006

Genetics

Genetic syndromes account for 5-10% of all colorectal cancers.[19,39] A large proportion of the young adults diagnosed with colorectal cancers have tumours that can be attributed to genetic syndromes.[39] Some studies have suggested that patients diagnosed at younger ages tend to have a more aggressive and advanced disease[40] although others are conflicting.[41]

A number of specific inherited conditions, which cause aggressive colorectal cancer have been identified. In these cases the cancer usually presents in young adulthood. The most common hereditary conditions are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). FAP results in colorectal adenomas in many patients by the age of 15 and in almost all by the age of 40.[39] Patients with HNPCC have a 70-85% risk of developing colorectal cancer and are at increased risk of cancers of the digestive and genitourinary system.[39] FAP and HNPCC patients develop a large number of adenomas; regular colonoscopy is required to monitor and remove these. The high probability of developing cancer in these patients often leads to preventative surgery to remove colon and rectum.

About 15% to 20% of colorectal patients may have a familial predisposition, without having a specific defined syndrome.[19,39] These patients have a close relative (1st degree) or history of colorectal cancer in the family and are twice as likely to develop colorectal cancer.[19] They may be at higher risk because of an, as yet, undermined hereditary syndrome. Alternatively, families may have similar lifestyles and therefore these cancers may be caused by similar environmental and lifestyles.

Obesity and physical activity

It is estimated that 3,000 colon cancers a year (10% of the total) are caused by obesity in the UK.[35] Obesity, independent of physical activity and other risk factors, is positively associated with colon cancer risk[34] and lower survival in colon patients.[42] Obesity is commonly measured as body mass index but certain types of obesity are especially strong risk factors. Central obesity as measured by the hip-to-waist ratio is strongly associated with colon cancer risk[34] and inversely associated with colon cancer survival.[42]

There is an inverse relationship between physical activity and risk for colon cancer, even after adjustment for obesity and diet.[34] However, analyses are difficult to interpret as individuals who are physically active tend to smoke less, use multivitamins, consume more fibre and consume less fat.[34] The biological mechanism for protection is also unclear, but physical activity may protect via a number of biochemical mechanisms including reduction of insulin resistance and hyperinsulinaemia.[34] In addition to preventing colorectal cancer, being physically active may also improve survival. A cohort studied in Australia found improved colorectal cancer survival in individuals who exercise regularly, particularly those with colon cancer stage II or stage III.[42]

Diet

A number of studies have investigated the association of colorectal cancer with diet, but the majority have been case-control studies which may suffer from recall bias, with inconsistent results. Studies of dietary intake have found vegetables to be protective however, it is unclear if the vitamin or fibre content is the protective factor. Some hypothesise that the increased fibre bulk and increased transit time associated with fruit and vegetables decreases the colon's exposure to toxins in the diet. Potentially protective dietary factors include fruits, vegetables, fibre and a diet low in red meat.[34] Intake of multivitamins, including folate, has been shown to decrease risk of colon cancer.[43]

Consumption of red meat may increase the risk of colorectal cancer although in some studies the results have been not significant.[33] Various mechanisms for the increased risk associated with red meat consumption have been suggested. The majority of the mechanisms for increased risk were associated with the high fat content of red meat. However, the relationship between fat intake and colorectal cancer has not been consistently shown.[33]

Other factors

In a meta-analysis of 8 cohort studies an increased relative risk of 1.23 (1.07-1.42) was found for individuals drinking more than 2 drinks per day on average.[36] There was no elevated risk for individuals drinking less than 2 drinks per day. Type of drink or gender had no effect on colorectal cancer risk. Smoking was weakly associated with colorectal cancer[38,39] but this effect may be confounded by the association between drinking and smoking.

There is increasing evidence of a protective effect of postmenopausal hormone replacement therapy.[37,44] For women on hormone replacement therapy, there appears to be a 35% decreased risk of colorectal cancer, which may last for up to 5 years after hormone use.[44]

Regular and short-term aspirin use decreased the risk of adenomas, with a relative risk of 0.8-0.5 depending on the dose.[45] A decrease in the risk of colorectal cancer has yet to be shown but is plausible.

Prevention

Individuals could reduce their risk by decreasing or eliminating exposure to risk factors. Identifying cancers at an early stage with screening or prevention in high-risk individuals by prophylactic surgery is estimated to reduce overall incidence by only 1.0% and mortality by 1.0% to 2.5%.[13] To have an impact on population incidence and mortality, interventions must reach a large number of patients. Screening is one of the most effective methods to identify colorectal cancer at the early stages, enabling early treatment and better outcomes and was initiated in the UK for people aged 60 to 69 by 2009.

Reorganisation of treatment services to provide the most effective and timely treatment possible is estimated to decrease mortality by 10% but cannot reduce incidence.[13] The decrease in mortality can be attributed to treatment by specialist staff, adherence to guidelines and collaboration of staff in multi-disciplinary teams. Increased use of adjuvant radiotherapy and chemotherapy will continue to improve survival and decrease mortality by a further 1-2% and 2-3% respectively.[13] These treatment protocols are included in guidelines already in use, therefore a further decrease in mortality should be occurring now or in the near future.

Treatment and clinical management

Overview

Treatment for colorectal cancer can include surgery, chemotherapy and/or radiotherapy. The modality and combination of treatment will vary depending on the sub-site, stage of disease and other clinical factors.

Surgery

Surgery is the most common treatment, either as the sole treatment or in combination with radiotherapy and/or chemotherapy. It is the only treatment with the potential of 'cure', and up to 40% of patients achieve cure after surgery.[46] In a population-based study in Yorkshire, during 1986 to 1993, 80% of patients received surgery.[47] Surgery removes the tumour and the associated segment of the colon or rectum, with its blood supply, regional lymph nodes and adjoining tissues. These are then assessed by the pathologist, and the pathological stage of disease ascertained, in conjunction with imaging. The stage of disease cannot be accurately estimated until after surgery (and pathology) at which point initial care plans may change. Pre-cancerous adenomas can be removed during colonoscopy and generally no further treatment is necessary.

Once the tumour and adjoining tissue are removed, the colon is reconstructed with a reconnection of the colon (anastomosis). Where there is a bowel obstruction and an anastomosis cannot be done at initial surgery and a colostomy bag may be fitted. For many patients a colostomy is temporary and the colon can be anatomised at a later time. Colostomies are more common for patients presenting as an emergency. Laparoscopic colectomy is now being used in some cases because it reduces the chance of infection, is less invasive, minimises the risk to the patient and decreases postoperative pain.[48-51]

Curative surgery for rectal cancer can be undertaken by anterior resection with total mesorectal excision or by a more extensive abdominoperineal excision. Mesorectal excision is now the recommended method of surgery but is dependent on the tumour being 5 to 9 cm above the anus. If the tumour is close the anus anterior resection is the preferred method. However abdominoperineal excision was still used in 27% of rectal surgeries during 1997 to 2004.[9] Generally, most of the mesentery will be removed during rectal surgery as it contains lymph nodes which may already be invaded by tumour cells and need to be checked for tumours cells in order to completely assess stage of disease. For some patients the rectum may be entirely removed and a colostomy performed however in some cases it is possible to remove the rectum and connect the colon directly to the anus. Surgery for rectal cancer has a high risk of leaks and less control over bowel function.

Palliative[a] surgery is undertaken to reduce symptoms including bleeding and blockages. In colorectal cancer patients, metastatases are most frequently found in adjacent organs or liver and these can be resected at the same time. If the tumour has invaded adjacent organs, removal may not be technically possible and a bypass (ileotransverse bypass) or faecal diversion through astoma can be done. If the patient is found to have unresectable late stage disease at laparoscopy, no further operative procedure may be offered (open-and-close). For some patients the most appropriate treatment may not be surgery due to metastatic (stage IV) disease at diagnosis, the location of tumour, comorbidities or a combination of these.[47]

Surgeon experience and specialist training may influence surgical outcomes, the choice of surgical technique and quality of surgery. Patients are treated by specialist colorectal surgeons, surgeons with high colorectal cancer case-loads or at high-volume hospitals generally have better surgical outcomes.[47,52-54]

Patients presenting as an emergency have more complications, including higher mortality, reoperation[b] rates and anastomotic leakages.[22] These patients tend to present at later stages but due to the urgent nature may not be treated by a specialist.

---

[a] Palliative treatment or care is not aimed at curing a patient but at reducing symptoms or pain, at slowing progression.

[b] Re-operation describes any subsequent surgery to repair a feature of the primary surgery. It may involve surgery at the same site, or at another site for the same condition.

Potential complications from surgery include infection, bleeding and adhesions that may lead to bowel obstruction in the longer term. Complications with anastomosis (rejoining of the cut ends of the colon after tumour excision) can also be carried out.

Radiotherapy

Radiotherapy is mainly used for rectal cancer. It is not recommended for colon cancer because the small intestine, which would also be irradiated, does not tolerate radiation well. Radiotherapy and chemotherapy are normally given in combination for rectal cancer, as chemotherapy makes the tumour cells more sensitive to radiotherapy. Long-course radiotherapy is used pre-operatively to shrink larger tumours for resection. Larger tumours (stage III) are generally treated for five weeks, with radiotherapy stopping a few weeks before surgery. For smaller tumours, a short-course of radio- and chemotherapy is usually performed the week before surgery which substantially decreases the chances of rectal cancer recurrence.[55]

In some circumstances post-operative radiotherapy may be offered to patients who haven't had pre-operative radiotherapy. It may be recommended if the tumour was difficult to resect or tumour cells are considered likely to remain, and will probably be used in combination with chemotherapy.

Chemotherapy

Chemotherapy may be given pre-operatively (neo-adjuvant therapy), to reduce tumour size and growth, or post-operatively (adjuvant therapy[c]), to decrease tumour size, slow tumour growth or treat and prevent metastasis. It can be given at a number of points during the patient pathway, including pre-operatively (to reduce tumour size), palliatively, post-operatively and adjuvantly. Adjuvant therapy is when a treatment is given to prevent potential metastatic disease but there is no evidence that metastatic disease is present. About 25% of patients experience a local recurrence after surgery, suggesting that microscopic tumours remained following surgery. These microscopic tumours may be eliminated with adjuvant chemotherapy.

More appropriate use of chemotherapy, the advent of 5-fluorouracil (5-FU) and new chemotherapy regimes, have produced better response rates and modest improvements

in survival.[56,57] For many years 5-fluorouracil (5-FU) and then 5-FU and folic acid given intravenously have been the standard chemotherapy treatment for colorectal cancer.[56] Adjuvant chemotherapy for stage III colon cancer is the standard treatment and improves survival but the benefit to stage II patients remains unclear.[56] Pre-operative neo-adjuvant chemotherapy decreases tumour size, resulting in improved colorectal resectability and in a reduction in hepatic metastasis.[56] Patients in stage I are not offered chemotherapy, but some stage II patients may be offered chemotherapy as part of a clinical trial. Rectal cancer patients may be offered chemotherapy and radiotherapy together pre-operatively for stage II and III tumours.

A newer platinum-based drug called oxaliplatin is recommended only for patients with liver metastases that may be resected following down-sizing.[58] For patients with advanced disease, 5FU with or without oxaliplatin or irinotecan is recommended.[58]

Lymph-node sampling is vital to identify patients who will benefit from adjuvant chemotherapy[59] but its frequency varies both internally and by hospital.[55,60] The accuracy of stage improves with an increasing number of lymph nodes sampled[61] (usually >12) but lymph node sampling is dependent both on the surgeon excising the tumour by wide margins (to maximise the number of lymph nodes), and on the pathologist testing and recording a large number of lymph nodes for tumour-positive status.

New treatments

A number of new treatments are aimed at reducing recurrence, including anti-inflammatory drugs, monoclonal antibodies and vaccines. Monoclonal antibodies are normally produced by the immune system but are produced in very large quantities in the lab to induce the patients immune system to specifically target tumour cells. However, they are expensive and not generally approved by the National Institute for Health and Clinical Excellence (NICE) which provides guidance and recommends treatment protocols. Monoclonal antibodies are not currently approved as first line treatment for colorectal cancer in the NHS but are sometimes prescribed in private treatment.[62,63] Cetuximab was one of the monoclonal antibodies NICE attempted to evaluate for first line treatment of metastatic colorectal cancer but the evaluation was terminated because the manufacturer did not submit evidence.

Follow-up

There are no guidelines for follow-up after colorectal cancer in the UK but patients generally receive regular check-ups and colorectal screening in the first year after surgery and the every five years up to age 75 years; however the impact on survival is not clear. Recurrence occurs in 2.4% to 40% of rectal cases[64] of cases.

Epidemiology

National

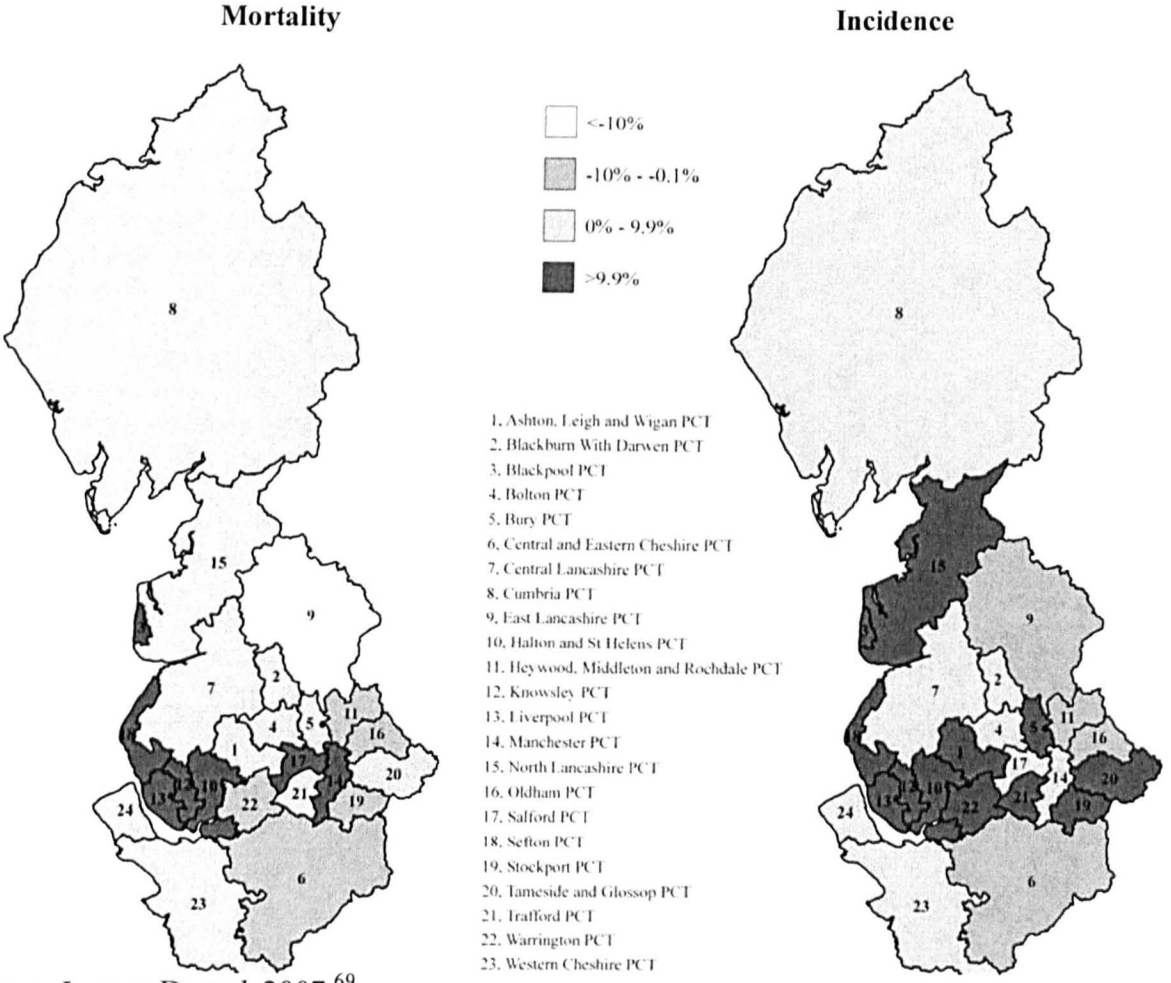
Cancer is one of the leading causes of mortality and morbidity in England, with one in three people developing cancer during a typical lifetime (aged up to 74-79 years). Colorectal cancer is the third most common cancer in men (second in women) and the third most common cause of cancer death, accounting for 28,000 cases and 13,000 deaths per year in England.[65] The annual number of incident colorectal cancer cases has increased by 20% for men and 5% for women in England from 1971 to 1997.[23] Conversely, mortality has fallen by 24% for men and 37% for women while 5-year relative survival has increased from 22% for colon cancer and 27% for rectal cancer in 1971-75[23] to over 47% in 1996-99.[1] These improvements have been attributed to both earlier diagnosis and improved treatment(s), most notably surgical techniques.[1,20,66] However, there are still large differences in survival regionally, nationally and internationally.

North West of England perspective

Incidence & mortality

The incidence of most cancers, including colorectal cancer, is higher in the North of England and Scotland, than the English average, probably due to the historic high levels of smoking, occupational exposures and socioeconomic deprivation.[67] For colorectal cancer men in the North West had significantly higher incidence and mortality rates than the UK and Ireland average but in women only the mortality rate in the North West was higher.[67] Colorectal cancer incidence and mortality were highest in the populated urban and socioeconomically deprived areas of the region, including Manchester, Liverpool, Salford, Sefton, Wigan and St. Helens[68] (Figure 1.4).

Figure 1.4: Standardised mortality ratio and standardised incidence ratio (SMR and SIR, %) in the North West of England relative to England (100%), men, 2001-2005.

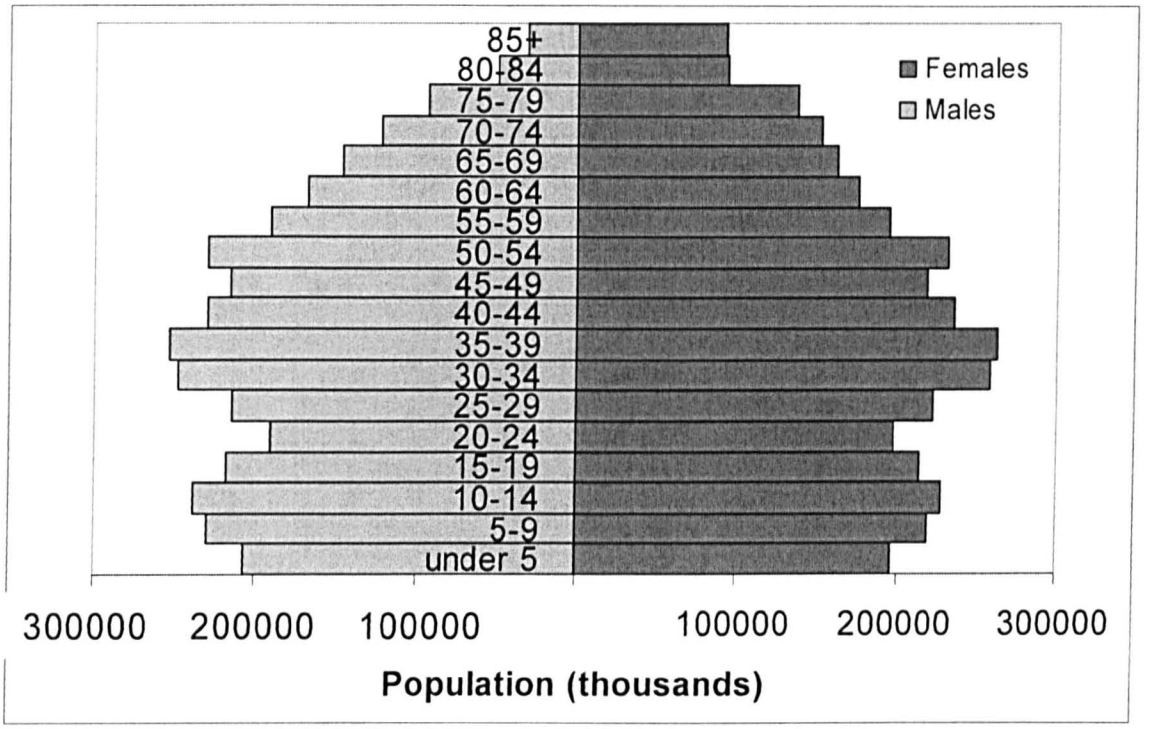


Source: Lemon D *et al.* 2007.[69]

Population

The North West has a population of 6.8 million with 48% men. The population distribution is typical of a developed country (Figure 1.5), with a small proportion in the younger age groups and the proportion in the older age groups increasing over time as the birth rate declines. Under the age of 20, there were more men than women but as the mortality rate in men increased with increasing age, particularly in the age range 15 to 29, the population of men is lower than women by the 20-24 age group. The mortality rate in men continues to be higher than women at subsequent ages and women continue to out-number men, with the difference increasing substantially in age groups over 70. In the oldest age group (85 and over) there was almost three times the number of women than men. The population in the 20-24 year age group is markedly lower than the younger and older population because these individuals may be away in higher education.

Figure 1.5: Population pyramid: annual average population for the North West of England, 1998-2003.

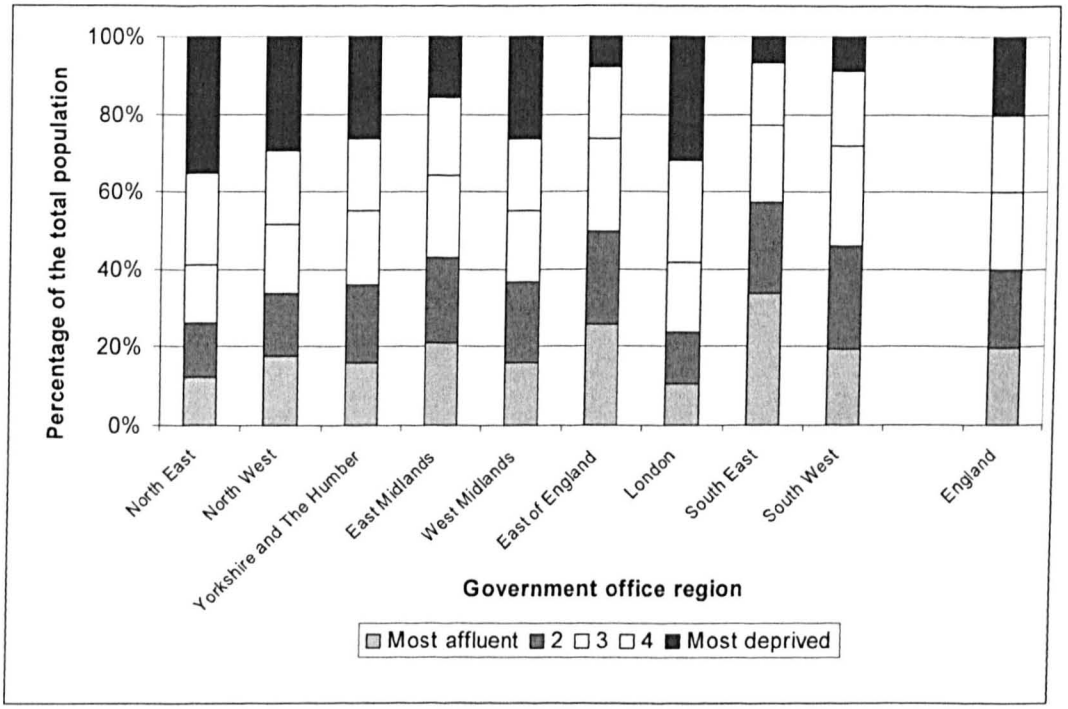


Source: Merseyside and Cheshire Cancer Registry, 2006

Socioeconomic deprivation

The North West has a high proportion of deprived areas relative to the English average, and over 50% (expected 40%) of the population in the two most deprived groups and 33% (expected 20%) in the most deprived group alone[68](Figure 1.6). Liverpool was the most deprived area in England with 72% of its population in the most deprived group. But conversely the North West also has many areas of affluence including Conglton, Cheshire, which had the highest proportion of the population in the most affluent group at 57% in England.[68] Within the North West the most deprived areas were Liverpool, Manchester and Knowsley and the most affluent areas were Cheshire, Conglton, Ribble Valley and Macclesfield.[68]

Figure 1.6: Percentage of the population by socio-economic deprivation category, England 2001



Source: Merseyside and Cheshire Cancer Registry, 2006

The North West had historically high levels of unemployment since the decline of the shipping and manufacturing industry in the 1980's. In 1991 Liverpool and Knowsley had the highest rates of unemployment in England at 36% and 26%, respectively.[70] Employment rates in the North West have improved to 58% compared to a national average of 61%.[71] However, the North West still has a higher than average unemployment rate at 5.1% with Liverpool having the highest in the North West at 11.1%.[71]

General Health

Indicators of health across the North West show a clustering of negative indicators around the deprived communities. "Binge drinking" was highest in Liverpool (27.8%), Knowsley (24.9%) and Manchester (24.8%) compared with the national average of 18.2%.[70] The prevalence of smoking mirrors that of binge drinking, with the urban centres of Knowsley (35.4%), Manchester (33.3%) and Liverpool (33.1%) having higher prevalence than the UK average.[70] Obesity rates are generally high in deprived areas, however adult obesity levels were low in Liverpool, Manchester and Macclesfield.[70]

There are a number of government financial schemes for individuals out of work or unable to work due to ill health, which are claimed at much higher proportions in the NW, particularly deprived in the deprived populations. Attendance allowance, which is paid to those over 65 with care needs or the terminally ill, was taken up by a higher proportion of the population in Liverpool, St Helens, and Knowsley than the national average but did not vary by deprivation.[68] In contrast incapacity benefit, which is paid to individuals who are unable to work due to disability or sickness, varies substantially by deprivation with those in the deprived group six times more likely to be claiming.[68] Liverpool, Manchester and Knowsley had incapacity benefit rates over twice the national average.[68]

Summary

The North West has higher incidence and mortality rates of cancer in general and colorectal cancer in particular than the English average. Part of this excess mortality may be attributed to the higher levels of socioeconomic deprivation, clustered in the urban centres. Overall health in the region is also worse than the national average, with the areas with the worst health also clustered in the urban centres. However, there is geographic and socioeconomic variation in health and cancer rates, with the rural and affluent areas in the region having much better health. Further quantification of the inequalities in survival and description of the influences on these inequalities will be discussed in the literature review.

Study rationale

Despite extensive long-term investment aimed at reducing inequalities in health, there remain substantial gaps in outcomes for many diseases, including colorectal cancer. The causes of these differences remain unclear. The remainder of this thesis will focus on variations in prognostic and clinical factors which may account for the socioeconomic differences in colorectal cancer survival.

(1) Coleman MP, Rachet B, Woods LM, Mitry E, Riga M, Cooper N, Quinn MJ, Brenner H, Estève J. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *British Journal of Cancer.* 2004; 90:1367-1373.

(2) Shack LG, Rachet B, Brewster DH, Coleman MP. Socioeconomic inequalities in cancer survival in Scotland 1986-2000. *British Journal of Cancer.* 2007; 97:999-1004.

(3) Schrijvers C, Mackenbach JP, Lutz J-M, Quinn M, Coleman MP. Deprivation, stage at diagnosis and cancer survival. *International Journal of Cancer.* 1995; 63:324-329.

(4) McArdle CS, Hole DJ. Outcome following surgery for colorectal cancer: analysis by hospital after adjustment for case-mix and deprivation. *British Journal of Cancer.* 2002; 86:331-335.

(5) Henley NC, Hole DJ, Kesson E, George WD, Cooke TG. Does deprivation affect breast cancer management? *British Journal of Cancer.* 2005; 92:631-633.

(6) Campbell NC, Elliot AM, Sharp L, Ritchie LD, Cassidy J, Little J. Impact of deprivation and rural residence on treatment of colorectal and lung cancer. *British Journal of Cancer.* 2002; 87:585-590.

(7) Schrijvers CT, Coebergh JW, van der Heijden LH, Mackenbach JP. Socioeconomic variation in cancer survival in the Southeastern Netherlands 1980-89. *Cancer.* 1995; 75:2946-2952.

(8) Madison T, Schottenfeld D, James SA, Schwartz AG, Gruber SB. Endometrial cancer: socioeconomic status and racial/ethnic differences in stage at diagnosis, treatment and survival. *Research and Practice.* 2004; 94:2104-2111.

(9) Morris E, Quirke P, Thomas JD, Fairley L, Cottier B, Forman D. Unacceptable variation in abdominoperineal excision rates for rectal cancer: time to intervene? *Gut.* 2008; 12:1690-1697.

(10) Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. *Annals of Oncology.* 2006; 17:5-19.

(11) Lyratzopoulos G, Sheridan GF, Michie HF, McElduff P, Hobbiss JH. Absence of socioeconomic variation in survival from colorectal cancer in patients receiving surgical treatment in one health district: cohort study. *Colorectal Disease.* 2004; 6:512-517.

(12) Hole DJ, McArdle CS. Impact of socioeconomic deprivation on outcome after surgery for colorectal cancer. *British Journal of Surgery.* 2002; 89:586-590.

(13) Scottish Executive Health Department. *Cancer Scenarios: An aid to planning cancer services in Scotland in the next decade.* Edinburgh: The Scottish Executive, 2001.

(14) Muto T, Bussey HJR, Morson BC. The evolution of cancer of the colon and rectum. *Cancer.* 1975; 36:2251-2270.

(15) Day DW. The adenoma-carcinoma sequence. *Scandinavian Journal of Gastroenterology.* 1984; 104:99-107.

(16) Schottenfeld D, Winawer SJ. Cancers of the large intestine. In: Schottenfeld D, Fraumeni JF Jr, editors. *Cancer Epidemiology and Prevention.* 2nd ed. Oxford: Oxford University Press, 1996, 813-840.

(17) SEER. Introduction to colorectal cancer. 2006. (cited 11 Feb. 2006) Available from URL: http://training.seer.cancer.gov/ss_module04_colon/unit01_sec01_intro.html

(18) Hamilton W, Round A, Sharp D, Peters TJ. Clinical features of colorectal cancer before diagnosis: a population-based case-control study. *British Journal of Cancer.* 2005; 93:399-405.

(19) Department of Health. *Guidance on commissioning cancer services: improving outcomes in colorectal cancer.* London: Department of Health, 1997.

(20) Faivre-Finn C, Bouvier-Benhamiche AM, Phelip JM, Manfredi S, Dancourt V, Faivre J. Colon cancer in France: evidence for improvement in management and survival. *Gut.* 2002; 51:60-64.

(21) Shack L. Analysis of symptom presentation in colorectal cancer patients in Merseyside and Cheshire. Shack L, editor. 2006. 30-6-2006.

(22) Wong SK, Kneebone A, Mogan M, Henderson CJA, Morgan A, Jalalundin B. Surgical management of colorectal cancer in South-Western Sydney 1997-2001: A prospective series of 1293 unselected cases from six public hospitals. *Australia and New Zealand Journal of Surgery.* 2005; 75:776-782.

(23) Hayne D, Brown RSD, McCormack M, Quinn MJ, Payne HA, Babb P. Current trends in colorectal cancer: site, incidence, mortality and survival in England and Wales. *Clinical Oncology.* 2001; 13:448-452.

(24) Cancer Research UK. UK Bowel cancer statistics. 2006. (cited 7 Oct. 2006) Available from URL: www.cancerresearchuk.org

(25) Gomez D, Dalal Z, Raw E, Roberts C, Lyndon PJ. Anatomical distribution of colorectal cancer over a 10 year period in a district general hospital: is there a true "rightward shift"? *Postgraduate Medical Journal.* 2004; 80:667-669.

(26) SEER. Anatomy of Colon and Rectum. 2006. Available from URL: http://training.seer.cancer.gov/ss_module04_colon/unit02_sec01_anatomy_fig02.html

(27) Quinn MJ, Babb PJ, Brock A, Kirby L, Jones J. *Cancer trends in England and Wales 1950-1999. (Studies on Medical and Population Subjects).* London: The Stationery Office, 2001.

(28) O'Halloran D, Guyers K, Henderson J. Notes on Anatomy and Oncology. Edinburgh: Elsevier Limited; 2004.

(29) International Union Against Cancer. TNM Classification of malignant tumours. 6th ed. New York: Wiley-Liss; 2004.

(30) Dukes CE. The classification of cancer of the rectum. *Journal of Pathology and Bacteriology.* 1932; 35:323.

(31) Astler VB, Coller FA. The prognostic significance of direct extension of carcinoma of the colon and rectum. *Annals of Surgery.* 1954; 139:846.

(32) National Cancer Institute. Colorectal cancer staging. 2008. Available from URL: http://visualsonline.cancer.gov/

(33) Norat T, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: dose-response meta-analysis of epidemiological studies. *International Journal of Cancer.* 2002; 98:241-256.

(34) Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer M, Willett WC. Physical activity, obesity, and risk of colon cancer and adenoma in men. *Annals of Internal Medicine.* 1995; 122:327-334.

(35) Bergström A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. *International Journal of Cancer.* 2001; 91:421-430.

(36) Cho E, Smith-Warner SA, van den Brandt A, Colditz GA, Folsom AR, Freudenheim JL, Giovannucci E, Goldbohm A, Graham S, Holmberg L et al. Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. *Annals of Internal Medicine.* 2004; 140:603-613.

(37) Boyle P, Langman JS. ABC of colorectal cancer: epidemiology. *British Medical Journal.* 2005; 321:805-808.

(38) Le Marchand L, Wilkens LR, Kolonel LN, Hankin JH, Lyu LC. Associations of sedentary lifestyles, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. *Cancer Research.* 1997; 57:4787-4794.

(39) Weitz J, Koch M, Debus J, Höhler T, Galle PR, Büchler MW. Colorectal cancer. *The Lancet.* 2005; 365:153-165.

(40) Adams J, Audisio RA, White M, Forman D. Age-related variations in progression of cancer at diagnosis and completeness of cancer registry data. *Surgical Oncology.* 2005; 13:175-179.

(41) Campbell NC, Elliot AM, Sharp L, Ritchie LD, Cassidy J, Little J. Rural and urban differences in stage at diagnosis of colorectal and lung cancers. *British Journal of Cancer.* 2001; 84:914.

(42) Haydon AM, MacInnis RJ, English DR, Giles GG. Effect of physical activity and body size on survival after diagnosis with colorectal cancer. *Gut.* 2006; 55:62-67.

(43) Giovannucci E, Stampfer M, Colditz GA, Hunter DJ, Fuchs C, Rosner BA, Speizer FE, Willet WC. Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. *Annals of Internal Medicine.* 1998; 129:517-524.

(44) Grodstein F, Martinez E, Platz E, Giovannucci E, Colditz GA, Kautzky M, Fuchs C, Stampfer M. Postmenopausal hormone use and risk for colorectal cancer and adenoma. *Annals of Internal Medicine.* 1998; 128:705-712.

(45) Chan AT, Giovannucci E, Schernhammer ES, Colditz GA, Hunter DJ, Willett WC, Fuchs C. A prospective study of asprin use and the risk for colorectal adenoma. *Annals of Internal Medicine.* 2004; 140:157-166.

(46) Scottish Intecollegiate guidelines network. Management of colorectal cancer: a national clinical guideline. Edinburgh: NHSScotland; 2003.

(47) NYCRIS. *Cancer treatment policies & their effects on survival; colorectal.* Leeds: NYCRIS, 2000.

(48) Leroy J, Jamali F, Forbes L, Smith M, Rubino F, Mutter D, Marescaux J. Laproscopic total mesorectal excision (TME) for rectal cancer surgery: long-term outcomes. *Surgical Endoscopy.* 2004; 18:281-289.

(49) Sasaki A, Nitta H, Otsuka K, Takahara T, Nishizuka S, Wakabayashi G. Ten-year experience of totally laparoscopic liver resection in a single institution. *British Journal of Surgery.* 2009; 96:274-279.

(50) NG KH, NG DC, Cheung HY, Wong JC, Yau KK, Chung CC, Li MK. Laparoscopic resection for rectal cancers: lessons learned from 579 cases. *Annals of Surgery.* 2009; 249:82-86.

(51) Colon Cancer Laparoscopic or Open Resection Study Group, Buunen M, Veldkamp R, Hop WC, Kudry E, Jeekel J, Haglind E, Pahlman L, Cuesta MA, Msika S et al. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncology.* 2009; 10:44-52.

(52) Wrigley H, Roderick P, George S, Smith J, Mullee M, Goddard J. Inequalities in survival from colorectal cancer: a comparison of the impact of deprivation, treatment and host factors on observed and cause specific survival. *Journal of Epidemiology and Community Health.* 2005; 57:301-309.

(53) Parry JM, Collins S, Mathers J, Scott NA, Woodman CBJ. Influence of volume of work on the outcome of treatment for patients with colorectal cancer. *British Journal of Surgery.* 1999; 86:475-481.

(54) Porter G, Soskolne C, Yakimets W, Newman S. Surgeon-related factors and outcome in rectal cancer. *Annals of Surgery.* 1998; 227:157-167.

(55) Quirke P, Steele RJC, Monson J, Grieve R, Khanna S, Couture J, O'Callighan C, Myint AS, Stephens RJ, Sebag-Montefiore D et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised trials. *Lancet.* 2009; 373:821-828.

(56) Lawes D, Taylor I. Chemotherapy for colorectal cancer - an overview of current management for surgeons. *European Journal of Surgical Oncology.* 2005; 31:932-941.

(57) McLeod A. Variation in provision of chemotherapy for colorectal cancer. *Journal of Epidemiology and Community Health.* 1999; 53:775-781.

(58) National Institute for Health and Clinical Excellence. *Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer; Review of technical appraisal 33.* London: NICE, 2008.

(59) Cox DE, Kellicut D, Adair C, Marley K, Otchy DP, Peoples GE. Sentinel lymph node evaluation is technically feasible and may improve staging in colorectal cancer. *Current Surgery.* 2002; 59:301-306.

(60) Ciccolallo L, Capocaccia R, Coleman MP, Berrino F, Coebergh JWW, Damhuis RAM, Faivre J, Martinez-Garcia C, Møller H, Ponz de Leon M et al. Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. *Gut.* 2005; 54:268-273.

(61) Pheby DFH, Levine DF, Pitcher RW, Shepard NA. Lymph node harvests directly influence the staging of colorectal cancer: evidence from a regional audit. *Journal of Clinical Pathology.* 2004; 57:43-47.

(62) *Improving outcomes in colorectal cancers: Manual update.* London: National Institute for Clinical Excellence, 2004.

(63) Department of Health. *Improving outcomes in colorectal cancer: the manual.* London: Department of Health, 1997.

(64) Mack LA, Temple Wj. Education is the key to quality of surgery for rectal cancer. *European Journal of Surgical Oncology.* 2005; 31:636-644.

(65) Office for National Statistics. *Cancer statistics: registrations (Series MB1 No. 34).* London: ONS, 2006.

(66) Mitry E, Bouvier AM, Estève J, Faivre J. Improvement in colorectal cancer survival: A population-based study. *European Journal of Cancer.* 2005; 41:2297-2303.

(67) Quinn MJ, Wood H, Cooper N, Rowan S. *Cancer atlas of the United Kingdom and Ireland 1991-2000. (Studies on Medical and Population subjects No. 68).* London: The Stationery Office, 2005.

(68) Wood J, Hennell T, Jones A, Hooper J, Tocque K, Bellis MA. *Where wealth means health: Illustrating inequalities in the North West.* Liverpool: North West Public Health Observatory, 2006.

(69) Lemon D, Flatt G, Shack L, Ellison T, Moran A. *Excess cancer mortality and incidence by PCT in the North West, 2001-05.* Manchester: NWCIS, 2007.

(70) Griffiths CFitzpatrick J. *Geographic variations in Health (Decennial Supplements No. 16).* London: The Stationery office, 2001.

(71) ONS. Census 2001. 2006. (cited 1 Sept. 2006) Available from URL: www.statistics.gov.uk/census2001

Chapter 2:

Inequalities in survival and prognostic factors

Overview

This chapter summarises the results of a systematic review of published literature on prognostic factors,[d] treatment and survival in colorectal cancer. The searches were limited to articles published since 1990.

Search strategy

Reproducible database searches of Pubmed,[1] EMBASE,[2] Web of Knowledge,[3] HMIC,[4] SIGLE,[4] Cochrane reviews[5] and Google Scholar[6] were conducted in January 2007. The title, key words and topic were searched for the terms defined in the text box below. Terms 3 and 4 were necessary to limit the search and were used in combination with a site description. Terms 1 to 4 combined were used sequentially with each of terms 5 to 8. The first and second search terms and pseudonyms, including rectum and colorectal, were used in all searches. The fourth term was used to limit the search to population-based studies, and to remove clinical trials.

Terms 1 to 4 were entered together

(1) Colon
(2) Rectum → or Colorectal or rectal
(3) Cancer
(4) Registry data or population-based

Terms 1 to 4 were then combined individually with each of the following:

(5) Grade
(6) Treatment or surgery or chemotherapy or radiotherapy
(7) Survival
(8) Comorbidity or comorbid

These searches were augmented by searches of the International Agency for Research on Cancer (IARC) publications list.[7] The bibliography in each reference was then

[d] Prognostic factors available include: sex, age, stage, grade, sub-site of tumour, tumour histology, place of residence, comorbidity and socioeconomic group.

reviewed by hand for relevant references. This process continued until no further references were found.

Survival

Colorectal cancer survival

Variations in survival between countries have mainly been attributed to differences in stage,[8,9] treatment[9] and socioeconomic levels.[10] Colon and rectal cancer survival has been lower in England than Europe,[11] and both are substantially lower than in the USA.[8,9] Over the past 30 years relative survival at five years after diagnosis for colon rectal cancer has nearly doubled in the England and Wales from 26% in 1971-75[12] to 47% in 1996-99[13] and is expected to improve to 52% for patients diagnosed in 2000-01.[13] Relative survival at five years for rectal cancer also increased with greater improvement occurring for women. There was a relative survival of 28% for rectal caner patients diagnosed during 1971-75[12] with survival increasing to 48.7% in men and 51.3% in women during 1996-99.[13]

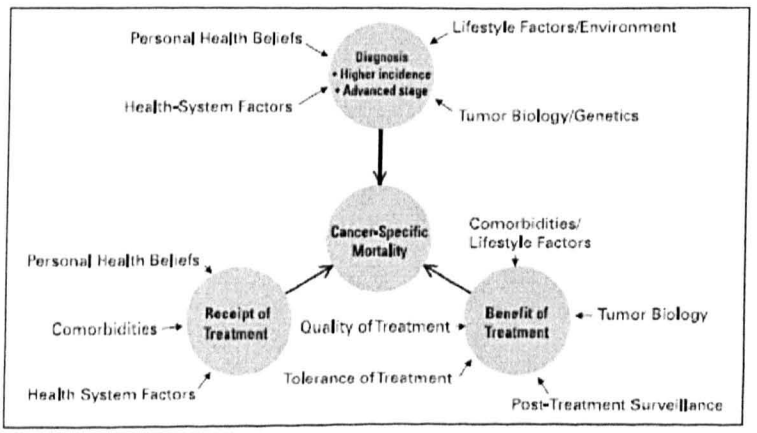
In the NW health region of England, colorectal cancer survival at five years was 4% to 5% lower than England and Wales for 1986-90, both within socioeconomic groups and overall.[12,14] There was variation in survival across the North West, with Greater Manchester and Merseyside and Cheshire health authorities continuing to have survival below the national average,[14] whereas Cumbria and Lancashire had colon cancer survival similar to England for cases diagnosed in 1995-97.[14] This pattern was not seen for other cancer types.

There is higher incidence and mortality[9,13,15] and lower relative survival[9,13,15-17] for patients living in deprived areas compared to patients living in affluent areas. In England and Wales during 1996-99, five-year relative survival for colon cancer was 5.4% higher for affluent men than for deprived.[13] For women the inequality in five year relative survival for colon cancer between affluent and deprived patients, or 'deprivation gap', was 8.3%. The deprivation gap was larger for rectal cancer patients, at 9.4% in men and 8.3% in women.[13] Survival has improved for colon and rectal cancer in all socioeconomic groups but the improvements have been greatest amongst patients from affluent areas. Between 1986 and 1999 the deprivation gap increased every five years by 1.9% for colon and 2.4% for rectal cancer in men (2.2% and 2.5% in women, respectively).[13]

The North West region contains a relatively high proportion of deprived areas and as a result has many more incident cases in the deprived group than the affluent. The North West also has some of the lowest cancer survival in England mainly due to the high proportion of deprived patients in the North West and the association of socioeconomic status with lower survival.[12]

Socioeconomic variations in colorectal cancer mortality, and hence survival, have been attributed to a complex interaction of clinical, health system factors, social and patient factors (Figure 2.1).[18] The inter-relationships of many of these quantifiable factors such as stage, age, grade and comorbidity on colorectal cancer survival have been studied with each having a section of the literature devoted to them. Whilst each of these factors directly influence survival they also influence which treatment is clinically appropriate. Treatment receipt may also be influenced by less quantifiable factors (e.g. general health, health knowledge, engagement in clinical process), either through the patients or physicians perception of its impact. For example, patients with poorer general health may believe treatment will be less effective and delay seeking health care or prefer a less invasive treatment. Alternatively, a physician may perceive that a patient with poor general health is unlikely to withstand surgery or chemotherapy. The influence of these qualitative factors on socioeconomic inequalities in survival are difficult determine, but may explain some of the residual socioeconomic inequalities in survival seen in some studies, even after adjustment for most clinical factors.[19,20]

Figure 2.1: Oncological health disparities model



Polite *et al.* [18]

International and regional comparability

Survival differences between countries and regions can be influenced by completeness and accuracy of registration. The impact of cancer registration completeness and

accuracy on the European and UK survival was evaluated by Prior *et al.* by modelling the effect on survival of excluding death certificate only (DCO)[e] cases, excluding clinically diagnosed cases and misdiagnosing *in situ* cases as malignant.[21] By excluding cases with only a clinical diagnosis researchers found survival estimates close to the European rates and suggested that survival differences between the UK and Europe could be partially attributed to incomplete registration by European registries.[21] It was suggested that European registries could bias their data and produce higher survival estimates by under registering cases diagnosed clinically or at death, as they are likely to be patients with poorer prognosis. However, more recent international studies have consistently found colorectal survival in the UK to be lower[22,23] indicating that differences in data collection only partially explains the lower survival, with the UK having a 'true' lower survival rate. For comparisons in the UK, these inconsistencies in data collection are not an issue as there is a nationalised standard method of registration which includes the registration of cases clinically diagnosed or diagnosed near death.

Stage

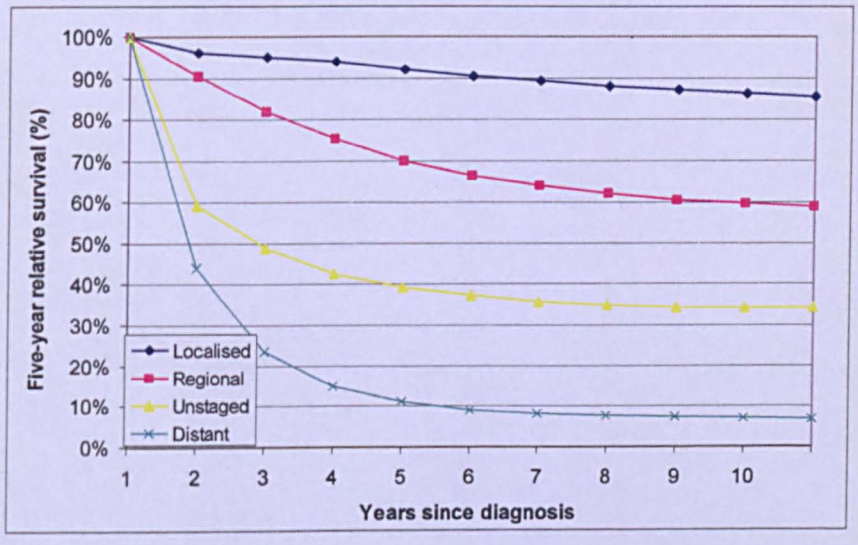
Late stage at diagnosis is strongly associated with poor survival for colorectal cancer patients (Figure 2.2). A population-based analysis, covering at least 14%, of US colorectal cancer patients diagnosed during 1996-2002 found patients with localised disease had a five-year relative survival of over 80% compared with 8% for patients in stage IV.[24] In Singapore a population-based study of colorectal cancer found five-year survival for patients with stage I-III improved from 25% to 66% for males (23% to 66% for females) between 1968-72 and 1988-92, but no improvement occurred for patients with stage IV disease.[25] Improvements in colorectal cancer survival over time may be partially attributed to the shift in stage at diagnosis, in addition to advances in treatment. Clinical audits in Dijon, France, and Glasgow, Scotland, found that there was a shift towards earlier stage between the 1970s and 1990s.[26,27] In Dijon the audit of 2,289 colon cancer patients found the proportion of cancers diagnosed in stage I and II increased from 40% in 1976 to 57% in 1991. Similarly an audit of 999 patients diagnosed during 1974-79 or 1991-94 and treated at Glasgow Royal Infirmary the proportion of colorectal cancer diagnosed in stage I or II increased from 31% in 1974-79 to 42% in 1991-94. Diagnosis at an earlier stage improves survival both because treatment is more effective and it adds a lead time. For some patients, with an aggressive cancer or other illnesses, diagnosis at an earlier stage will not delay the time

[e] Death Certificate Only (DCO) registration occurs when the only information about a patient is found on the death certificate.

of death. In these patients diagnosis at an earlier time increases survival but does not influence the ultimate outcome or time of death thereby adding lead time.

There is conflicting evidence on whether patients from deprived socioeconomic groups present at later stages.[16,17,28-31,31-33] Some studies have found an association between lower socioeconomic status and late stage tumours[28,29] while others have found no association.[16,17,31,33,34] Stage at diagnosis is an important prognostic factor for survival[8,33,35] but even after adjusting for stage at diagnosis deprived patients had lower survival.[16,17] A study of outcomes after colorectal cancer surgery in Central Scotland, for patients diagnosed during 1991-94, found that after adjusting for stage, the majority of the excess mortality in lower socioeconomic groups was post-operative mortality, most notably after curative surgery.[16]

Figure 2.2: Five-year relative survival by stage at diagnosis for colorectal cancer, all ages, all races, 1988-2002, USA



Source: Surveillance Epidemiology and End Results, Fast Facts, USA, 2006[36]

Deprived patients are more likely to present as an emergency.[17,37] Patients presenting as emergencies have lower survival than non-emergency patients[37] which may support the hypothesis that deprived patients are diagnosed at a more advanced stage or have more comorbid conditions. Few studies have been able to adjust for all the important prognostic factors; possibly due to the large sample size necessary. However, an audit study of patients diagnosed in Wessex, England, adjusted for most factors and found socioeconomic inequalities persisted after adjustment for age, sex, stage, co-morbidities and treatment.[17] Socioeconomic inequalities in colorectal cancer survival were also

found in a population-based London study during 1980-1989.[38] These variations could not be explained by stage.

It has been suggested that deprived patients may be more likely to have 'occult'[f] metastasis[16] which could explain why residual inequalities in survival remain even after adjusting for most prognostic factors. Occult metastatic disease may be more common in deprived patients because there is a i) biological differences in tumours ii) poorer general health in deprived patients iii) diagnostic assessments are less thorough in deprived patients and metastatic disease. There is evidence that patients from different socioeconomic groups do tend to have different histological and sub-sites of colorectal cancer, with the deprived groups having more distal cancers and adenocarcinomas, although no socioeconomic differences in survival were seen.[31] There has been little published work on biological variations by socioeconomic group for colorectal cancer. Comorbidity has been associated with deprived patients in many studies.[34,39,40] Deprived patients may be more likely to have poorer overall health because of higher prevalence of lifestyle factors, even without specific comorbid conditions, that may compromise the immune systems ability to fight or prevent illness.[41] Lower levels of surgery may explain both the higher proportion of missing data for stage and lower survival in deprived patients however, whether lower surgical rates are clinical appropriate is difficult to determine.

Treatment regimes are stage-specific.[42,43] Complete staging requires both wide margins to be excised by surgeon and multiple lymph node sampling to be conducted by the pathologist. Complete staging is mainly done at the same time as surgery[44] but staging is sometimes done clinically, by CT or MRI. For rectal cancer patients, tumour size from the TNM staging system was most predictive of survival whereas nodal status predictive of the likelihood of recurrence.[45] Sufficient lymph node sampling and staging was most likely with specialist treatment but there is a correlation between specialist treatment and affluence, with affluent patients being most likely to be admitted to a high volume hospitals.[37] In addition, the proportion of patients having surgery is also higher in more affluent patients.[37] Consequently, deprived patients are more likely to have missing stage information.[46]

[f] The spread of cancer cells from the primary site with secondary tumours that are too small to be clinically detected at the time of diagnosis (micrometastasis).

Missing stage

For some patients, staging information is missing or unavailable, either because the information was not available to the cancer registry or because stage was not recorded. Frequently, patients with late stage tumours have missing data for stage because detailed staging was not required for curative treatment. Patients without a stage are older, later stage and deprived[46-48] and generally have an intermediary survival experience between early (Stage I) and advanced stage (Stage IV) indicating there is a mix of stages in the unknown and missing category (Figure 2.2). Most cancer registries have a large portion of cancers with missing data for stage making it impossible to produce stage-specific survival for these patients.[49] Unfortunately, colorectal cancer symptoms are non-specific or absent until the later stages therefore many patients will present late in the course of disease.

Subdivision of stages

Patients in stage III have a mixed prognosis, with some responding well to treatment and others, likely those with distant metastasis, not responding to treatment.[50] Some studies and staging systems[51] have subdivided stage III to distinguish differing prognosis.[50] Sub-division of stage III into three groups, based on tumour invasion in patients without metastatic disease, was found to produce substantial differences in survival rates of 80%, 60% and 30% at five years.[50] Subdivision by tumour and nodal status was less effective, and produced only two groups with 60% and 30% survival.[50] The three stages determined using tumour status were effective at identifying heterogeneity in stage III patients and may be clinically useful as the further subdivision identified patients in stage III who may have survival probabilities similar to stage II patients.[50]

Grade

There are very few epidemiological studies of grade and survival in colorectal cancer patients. Poorly differentiated tumours were associated with decreased survival.[52] This may be particularly pronounced in the elderly with post-operative mortality higher in patients aged over 80 and highly undifferentiated cells (grade III and IV).[53] Stage is a stronger prognostic indicator than grade with most studies incorporating some measure of stage rather than grade.

Ethnicity

Ethnicity is strongly associated with many factors including migration, socioeconomic status, culture, environmental exposure, income and childhood experience.[54] Ethnic groups in some regions, particularly the US, can be closely associated with lower socioeconomic status. Incidence, mortality and survival have been shown to vary by ethnicity in the US[18,20,33,55-58] but there is little published work in the UK. Certain ethnic groups, particularly Jewish populations, are known to be at higher risk of cancer due to genetic mutations[59,60] but these have been related to incidence, rather than survival. A population-based study, covering up to 14% of the US colorectal cancer patients diagnosed during 1975 to 1999, identified socioeconomic differences within ethnicity groups, with affluent patients having survival up to 10% higher than deprived.[33] However, when ethnic groups in the USA received equivalent treatment responses are similar.[61,62]

Historical diet is an important risk factor for colorectal cancer, however there is little or no work on the diet and ethnicity. Particularly relevant may be nutrition in early childhood which for many ethnic individuals would have occurred outside their current country of residence. As the variations in survival by ethnicity are so large and wide-spread it is unlikely to be due only to genetics but the interplay of many factors, with the importance of each factor also varying by ethnic group. Data on ethnicity in UK is poor and in the North West only 3% are an ethnic minority making analysis by ethnicity not possible in this study.

Comorbidity

Comorbidity, or illnesses other than the colorectal cancer, may vary by demographic factors and are more common in patients who are older[39] and of lower socioeconomic status.[17,63,64] Comorbidity may affect how clinically appropriate and effective treatments can be, therefore, it is necessary to adjust for comorbidity to make accurate comparisons of survival. Comorbidity measures are regularly recorded in clinical and audit studies through case note review or patient assessment at diagnosis. Measuring comorbidity for population-based data can be more challenging because of the number of cases. In most population-based cancer registry data administrative datasets are used to measure comorbidity, while practical these datasets may have problems with bias, inaccurate coding and coding or system changes over time. There is no 'gold standard' method for measuring comorbidity various methods based on: time spent in hospital (bed-days),[64]

previously diagnosed diseases (e.g. asthma, diabetes, arthritis)[65-68 69] or scoring based on clinical judgement.[70] The most widely used and validated method[67,71] was developed by Charlson *et al.* in 1987[66] and is based on previously diagnosed illnesses. The Charlson comorbidity score is a weighted summary score originally developed to reflect the relative risk of death at one year for medical inpatients in a New York hospital and validated on breast cancer patients at another hospital.[66] It has since been validated on larger studies of cancer patients[39,71,72] and other diseases[67,68,73-76] which have found it to be a robust and accurate measure of comorbidity.

Deprived cancer patients tend to have higher levels of comorbidity[17,63,64] and emergency hospital admission[37,64] than affluent patients. Both are independently associated with lower survival. In the North West region, deprivation was associated with increased hospitalisation rates for colorectal cancer.[77] Deprived patients were twice as likely as affluent patients to be admitted as an emergency rather than as an elective hospital admission.[32,37] After adjusting for comorbidity, differences in colon and rectal cancer survival by socioeconomic status remain,[32,64] but they are larger for colon cancer and may be non-significant in rectal cancer.[64]

Co-occurrence of colorectal cancer with other conditions, such as heart disease, pulmonary disease and diabetes,[78] is unsurprising because the risk factors are similar or overlapping, with increased risk associated with environmental and lifestyle factors. The most commonly identified comorbid conditions for colorectal cancer patients are cardiovascular disease, chronic obstructive pulmonary disease (COPD), hypertension, diabetes and previous cancers. These associations are consistent regardless of methodology.[34,39,79,80] Cardiovascular and COPD significantly lowered survival[39,80,81] however, the impact of other illnesses on survival was not consistent. A case-control study in Hong Kong found increased risk of colorectal tumours in patients with coronary artery disease (CAD), metabolic syndrome and a history of smoking,[78] although it is unclear if this is solely due to the overlapping risk factors for these conditions.

Comorbid conditions in colorectal cancer patients increase the complexity of treatment, particularly surgery, and decrease survival[26] and life expectancy.[80] The severity and number of comorbid conditions increases with age.[34,39,39,71,79,81] In a population-based study of colorectal patients diagnosed between 1993-95 and registered at Eindhoven

cancer registry, Netherlands, 26% of men (34% of women) under 70 at diagnosis had comorbidity, but that increased to 51% of men (56% of women) over 70 at diagnosis.[39] The highest level of comorbidity was associated with tumours of the ascending colon at 52% and decreased along the large colon to 44% for cancers of the rectum. Comorbidity did not effect surgery rates but was associated with lower short-term survival.[39] The increase in comorbidity in elderly patients makes clinical management more complex and influences prognosis.

A registry-based study in Eindhoven, Netherlands of colorectal patients diagnosed during 1993-95, found an association between stage at diagnosis and comorbidity after adjustment for age.[39] Higher rates of comorbidity occurred in patients diagnosed at an earlier stage which was attributed to an incidental diagnosis of early colorectal cancer while receiving regular monitoring for a concomitant condition,[39] or a detection bias. Even after adjusting for stage and age, both survival and life expectancy decreased consistently with increasing comorbidity.[39,39,80] A population-based study in the USA during 1993 to 1999 which covered 14% of the country found stage-specific life expectancy decreased with increasing comorbidity even after adjustment for age. Men diagnosed at age 81 with stage I colorectal cancer and no comorbid conditions had a life expectancy of over 10 years (14 years for women) but this decreased to 4 years for men with 3 or more conditions (5 years for women).[80] The strong association between comorbid conditions and survival highlights the importance of adjustment for comorbidity when evaluating other factors, such as age or stage, in epidemiological studies.

Age

Survival from colorectal cancer decreases with increasing age[17,32,32,82-84] but this is particularly pronounced for survival at one year.[25,83] Lower short-term survival in the elderly may be due to various factors, including late presentation and comorbidity, which can influence the clinical appropriateness of treatment. Clinical guidance does not exclude elderly patients from treatment,[43,85,86] but the presence of comorbidity may influence whether a given treatment is appropriate. The proportion of elderly patients offered treatment, including adjuvant and palliative care, seems to have increased over time in the Côte-d'Or region, France,[26] and in a meta-analysis of colorectal cancer treatment in the elderly[87] but this may in part be due to an improvement in the general health of elderly patients, enabling more curative treatment. A literature review of

treatment concluded that curative treatment in the elderly did not lead to higher rates of complications or toxicity compared with younger patients,[87] and that survival from curative surgery was similar regardless of the patient's age. There is less trial evidence for the appropriateness of specific treatments in elderly patients, because most clinical trials are limited to patients under 75.[87] Although the data on older ages is limited, in a trial for breast cancer the effectiveness of treatment was not modified by age.[88] Breast cancer surgery for older women has evolved over time from avoiding surgery, to preference for mastectomy to breast conserving surgery, which generally always occurred for younger patients.

A meta-analysis of colorectal cancer treatment in the elderly concluded that older patients were more likely to delay appointments, and to present at a later stage.[87] Treatment delays in elderly colorectal cancer patients were also found in a survey of cancer patients in England and Wales during 1999 to 2000.[89] However, active treatment may not be implemented for elderly patients due to patients' or physicians' beliefs about the ability to withstand treatment, or about life expectancy. A population-based study of colorectal cancer patients diagnosed during 1986 to 1994 in Yorkshire found lower rates of treatment in elderly patients,[32] although some studies have found elderly patients were more likely to have missing data on treatment which may have influenced these analyses.[32,48] Even if treatment is not intended as not curative, treatment substantially improved survival and without increasing the proportion of adverse effects in elderly patients.[87] In a population-based study of colorectal cancer patients diagnosed between 1976 and 1998 in the Côte-d'Or region, France, the proportion of patients receiving surgical resection increased from 69% to 91% over the period with the largest increases in the elderly (56% to 90%).[26] Increasing levels of surgery in older patients may be partially due to shifts toward earlier stage at diagnosis and fewer comorbid conditions but it is unlikely the magnitude of these changes explains the increase in surgery.

Some degree of ageism in the treatment of the elderly likely occurs either because of perceived life expectancy, quality of life or the impact of comorbidity. In the UK, age was associated with treatment delays in the elderly[89] and lower rates of treatment.[32] Elderly patients are more likely to have missing data, such as stage and treatment, which makes comparison of clinically appropriate treatment regimes difficult.[48] The influence of a patient's perception of these and the influence of their physician on the patient's treatment choices is less clear. Most studies of patient choice have consistently

found most patients prefer to take a passive role in treatment decisions and relying on their physician to make the decision.[90] This is evidence to suggest that the treatment decisions are not directed by patient refusal.

Gender

Many studies in the UK have found that women have higher survival for colon[32,82,91] or rectal[13] cancer, although this has not been found in all studies.[12] The survival advantage among women has been attributed to differences in immunological responses to surgery.[91] Testosterone had a detrimental effect on the immune response to trauma,[92,93] but female sex hormones had a positive impact on the immune responses.[94]

Rurality

In rural communities the inequalities differ dramatically from those of urban because the organisation, availability and range of health services offered will be different from that of an urban or suburban area.[95] Colorectal cancer patients living in rural settings were seen sooner, but were less likely to receive radiotherapy[96] and surgery.[26] The excess travel and different accessibility experienced by rural patients may influence diagnostic and treatment choices and living farther from a cancer centre was associated with lower survival[82,97] and a higher chance of being a DCO.[97] This is supported by the evidence that rural patients presented with more advanced disease at diagnosis[98] and their treatment was not as well managed compared to urban patients.[99] As a result there are differences in colorectal cancer survival in patients resident in urban compared with rural areas, even after adjustment for socioeconomic factors.[97] Patients living in a rural setting had 5-year survival 11% lower than urban settings.[97] However, these studies were based in Scotland where rural communities can be very isolated and travel times longer than in England, and may not be directly comparable to England. While the degree of difference may not be as extreme, rural and urban differences are likely to also exist in the North West.

Other factors

Lifestyle factors, such as diet and exercise, are risk factors for colorectal cancer but there is little work on the impact of these on survival. A case-control study of colorectal cancer in France found five-year survival was improved by a diet high in energy, however there was no effect on survival at ten years.[100] Physical activity, body mass

index[g] and food type had no effect.[100] This study alludes to a possible effect of diet on five-year survival, but it has many methodological problems including small sample size, lack of cause of death information and recall bias. It is most likely that diet is associated with other factors, such as overall fitness and lack of co-morbidities, which influence treatment options and survival directly.

Socioeconomic status

In the UK there are wide variations in life expectancy by socioeconomic status. Deprived individuals have a life expectancy on average 5 years less than the most affluent individuals.[101] The North West has the lowest life expectancy in the UK for men and second lowest for women, a pattern mainly attributed to the geographic patterns of socioeconomic deprivation.[101] Socioeconomic status is a proxy for exposure(s) and lifestyle, including diet, physical activity, environmental factors, smoking and drinking status, which are all risk factors for colorectal cancer. Lower socioeconomic groups have higher exposure to disease (and cancer) risk factors, including smoking, obesity, high fat foods, lower fruit and vegetable consumption,[102] higher alcohol consumption and lower levels of physical activity.[77] As a result, residents from lower socioeconomic groups are more likely to report their health as "not good" than more affluent residents.[103] There may also be an association between low socioeconomic status and lower levels of access to health services and specialists. Unfortunately, variations in outcome by socioeconomic groups are widening for many diseases, including cancer,[13] which has contributed to a widening of the life expectancy differences.

Socioeconomic inequality in biological aging has been proposed as a possible contributing factor to socioeconomic inequalities in survival.[41] This could occur when accumulation of cellular damage, including genes, occurs as people age, but this process could be increased by exposure to environmental factors, like smoking and radiation. Patients in lower socioeconomic groups may be disproportionately exposed to these factors, thereby accumulating more cellular damage and having a higher risk of cancer and worse prognosis due to co-morbidities.[41] Deprivation has been associated with younger age at diagnosis for colorectal cancer,[41] which may support this hypothesis.

[g] Body Mass Index is a measure of ideal weight

While patients may be interested in the absolute inequalities to compare differences across region and other variables it is necessary to adjust for socioeconomic status and other variables that differ by socioeconomic group (age, stage, comorbidity). For relative survival analysis, it is necessary to create socioeconomic-specific life tables to take account of underlying differences in life expectancy. Failure to do this would result in an inaccurate estimate of the survival gap as the underlying mortality would not be representative of the population from which patients derive.[104] Socioeconomic differences in relative survival are reduced when socioeconomic group specific life tables are used.[104]

Measuring socioeconomic status

There are a number of ways to categorise the socioeconomic status of individuals. Socioeconomic measures can be based on individual level data such as employment type, education level and income. Historically, socioeconomic assessments were done using these data, but in practice, holding sensitive information like this is rarely done and can be easily biased by self-reporting.

Alternatively, ecological methods for determining socioeconomic status are increasing in popularity. Many ecological socioeconomic measures are available including Carstairs' index,[105] Index of Multiple Deprivation 2000[106] and 2004,[107] the Jarman under-privileged area score[108] and the Townsend Deprivation Score.[109] Regardless of the type of deprivation measure used, a deprivation gap in survival persists, but the magnitude of the differences varies.[110]

Ecologically defined socioeconomic measures are based on the area in which a patient lives, usually at diagnosis. Routinely recorded measures associated with geography can be used to assign socioeconomic measures based on regular surveys including the decentennial census, the Health and Lifestyles Survey[111] and the British Household Survey.[112] In the past, measures based on the voter turn-out, subscribers/donors for charities and government surveys have all been used.[113] Index of multiple deprivation is currently the most common method and is based on regularly recorded administrative data for the seven domains of: income, employment, health deprivation and disability, education skills and training, barriers to housing and services, crime and the living environment. Prior to 2001 socioeconomic status was measured at each census.

Socioeconomic inequalities in survival are influenced by the geographic area used to assign the index, but not by the socioeconomic index used.[110] Ecologically defined socioeconomic categories have been assigned at various geographic sizes and levels including census enumeration district (ED), lower level super-output area (SOA) and electoral ward, which consist of an average of 440, 1500 and 6000 residents, respectively.[110] Measures based on ward are available for all census years while ED is available for 1991 and SOA is available for 2001. Deprivation measures based on small areas (ED, SOA) were highly correlated with individual level of deprivation but larger area measures (wards) were more heterogeneous thereby averaging the inequalities and diluting the final measure.[114] Deprivation measures based on larger populations (wards) result in smaller socioeconomic differences in incidence[115] and survival[110,116] and are not good predictors of health.[114] Additionally, ward population size varies from 100 to 30,000 people resulting in an inconsistent measure of socioeconomic status.[110,116] Smaller area measures, both SOA and ED, produced socioeconomic differences which were 25% larger than with ward measures.[110] It is also important that the size of geographic unit is similar over time to avoid changes due to alteration in geographic groupings and the associated dilution effects.

A comparison of ward- and SOA-based geographic units for assigning socioeconomic group was analysed with national incidence data.[115] Socioeconomic score, a sum of the census measures, was assigned to a geographic area (SOA or ward). The geography was then ordered sequentially in ascending order (affluent scores to deprived scores) and grouped into five categories. Categories were grouped by populations, so that a one fifth of the population (9.8 million) is in each group, or into equal numbers of ward or SOAs. Grouping by population was found to produce consistent and larger deprivation differences for incidence.[115]

A registry-based study in England of the methodology of ecological socioeconomic measures compared the use of ward- and SOA-based socioeconomic measures in survival analysis of colorectal cancer. Their findings were consistent with other studies[110] based on SOA level measures producing a consistent inverse relationship with survival and a larger number of significant deprivation gaps. Regardless of the measure used, there has been consistent improvement in the survival within each socioeconomic group but there is no evidence that the deprivation gap is decreasing.[116] The deprivation

gap for colorectal cancer was mainly due to the large deprivation gap in patients under 70 at diagnosis (9.3%).[116]

Ecological socioeconomic groups are defined based on area of residence. As socioeconomic status is based on area of residence at diagnosis it may not necessarily be representative of the patients' current or historical socioeconomic group. Generally, people living in the same area have similar levels of deprivation but this may not be true for all individuals. Additionally, the affluence and hence socioeconomic category, a patient currently lives may be very different to their historic socioeconomic status. This is particularly relevant for cancers where exposure to risk factors occurs years or decades before cancer diagnosis. Some argue that patients' illness may result in economic hardship and cause a shift to lower socioeconomic group rather than a lower socioeconomic group being a risk factor for diseases.

Treatment

Most colorectal cancer patients receive some form of surgery, radiotherapy and/or chemotherapy treatment.[52] Treatment regimes and combinations have evolved over time as new equipment, techniques, and drugs have become available.

Surgery

After adjustment for stage and socioeconomic status, differences in survival have been attributed to differences in surgery.[13,26,84,117] Recent improvements in surgery include new approaches to surgical excision (e.g. total mesorectal excision, laparoscopic surgery), greater standardisation of treatment protocols, improvements in surgical technique, and peri-operative treatment.[27] Improvements in surgery have been attributed to increased use of in antibiotics, better management of anaesthesia and fluid balance, decreased blood loss, wider tissue dissection, and most notably radical resection of the circumferential margin.[27]

A hospital-based study of colorectal cancer patients in Glasgow, Scotland, in 1974-1979 and 1991-1994 found that more patients in 1991-94 received curative surgery and fewer palliative surgery, with both curative and palliative surgery patients having better survival.[27] Post-operative mortality also decreased from 14% to 9%, due to improvements in peri-operative care. The study concluded that improvements in peri-operative care had led to fewer anastomotic leakages and abscesses, possible due to increased use of antibiotics and treatment by specialists.

A population-based study of colorectal patients in the Côte-d'Or region, France, during 1976 to 2003 found the proportion of patients resected for cure increased over time both for patients with localised disease and for patients with distant metastases.[84] Patients with colon cancer were more likely to undergo resection than rectal cancer patients. Improvements in long-term survival were only seen in patients undergoing curative resection.

Surgical outcomes may be effected by their surgeon experience and specialist training, which may influence the choice of surgical technique and quality of surgery. Surgical outcomes are improved when patients are treated by specialist colorectal surgeons, surgeons with high colorectal cancer case-loads or at high-volume hospitals.[17,32,118,119] The type of surgery received has a striking effect on patient outcomes. Patients who received total mesorectal excision (TME) anterior resection for rectal cancer had significantly lower recurrence rates, and higher survival than those who received blunt dissection.[85,120,121] TME decreased recurrence and anastomotic leakage, and improved sphincter control and survival.[32,120]

Surgeon-related factors

Surgical outcomes are better when patients are treated by specialist colorectal surgeons, surgeons with high colorectal case loads and/or high-volume hospitals.[17,32,118,119] Patients treated by these surgeons are more likely to have a histologically confirmed diagnosis, and to receive surgical treatment and adjuvant chemotherapy.[32,122] Active treatment was higher for patients treated by surgeons with high case-loads. Active treatment was 93% for patients treated by high-volume surgeons compared to 81.5% in low-volume surgeons.[32] However, this may be an over-estimation because there was no adjustment for case-mix and patients with a particularly bad prognosis are more likely to be treated by a local surgeon rather than referred on to specialist services.[32]

Some studies of the effect of high-volume surgeons and surgeon specialisation have found conflicting results,[32,45,119] but these may be attributed to differences in definitions or sample size. A population-based study of all patients diagnosed in the Northern and Yorkshire region of England found that patients had better management and outcomes in high-volume hospitals or with high-volume surgeons.[32] The study defined high-volume hospitals as those treating more than 128 cases per year and high-volume

consultants were defined as those who treated more than 36 patients per year. There was also a gradient in post-operative mortality by socioeconomic group with deprived patients having from 0.4% to 2.7% higher mortality depending on the sub-site of cancer.[32] Recurrence was not evaluated in this study. This was the largest study and had the highest case-load defining high-volume surgeons, therefore may be the most easily transferable across the NHS.

A study based at five hospitals in Edmonton, Canada, between 1983 and 1990 found higher survival and lower local recurrence for patients treated by a colorectal specialist or high-volume surgeon.[119] They defined high-volume surgeons as those treating more than 21 patients and specialists as those trained in colorectal surgery. Similarly, a case-note review study of 673 patients in the mid-western USA with stage II or stage III rectal cancer[45] also found high-volume surgeons, defined as over 10 cases per year, had lower recurrence rates.[45]

A study of 927 colorectal cases diagnosed during the first half of 1993 in the Greater Manchester area of England found an association between hospital volume and survival, but consultant volume did not significantly affect survival.[118] In contrast to the other studies mortality increased with the increasing number of operations undertaken by consultants, even after adjusting for age, stage, sex and site of tumour.[118] This may be due to higher mortality rates for high-volume consultants because they are undertaking more complex cases. This study was carried out in 1993, prior to the release and implementation of colorectal cancer clinical guidance, and may not represent the current situation.

A Swiss study of patients entered in two colorectal cancer trials during 1981 to 1993 found surgeon training level (certified vs. in-training) and training hospital (university vs. non-university) were not associated with survival or local recurrence, but case-load at both surgeon and hospital level was associated with increased survival and lower probability of local recurrence.[123] In Switzerland, the majority of patients are treated by general surgeons, so the direct comparability with the UK's system of specialised treatment may not be appropriate. However, the main difficulty in the transferability of findings is the low threshold of 5 cases per year used to determine high-volume surgeons and 26 cases per year for high-volume hospitals.

Improved outcomes when treated by specialists and high-volume surgeons have been attributed to their higher likelihood of following treatment guidelines and more extensive lymph node harvesting which enables accurate staging and treatment.[124] Ensuring that patients are treated by these specialists, and surgeon availability, vary by hospital and region.[32] It may be particularly difficult to ensure specialist treatment and surgery for cases presenting as an emergency, especially for initial surgery.

The evidence on high-volume or teaching hospitals having lower post-operative mortality and higher long term survival is less clear, but any effect is likely to be a 'proxy' for training and or the experience of the treating physicians.[122] The definition of high-volume or specialty hospital seems to be key in determining survival and treatment differences. Two Swedish studies identified improved survival and adherence to treatment protocols in university hospitals and general district hospitals.[125,126] The majority of studies have focussed on volume as a measure of the surgeons skill, expertise or quality of treatment[122] but the exact volume needed is not clear. The complexity of surgery was not accounted for in any of the studies but may be argued that surgical choice is influenced by experience. Workshops on surgical technique and national education programmes aimed at improving surgeon skills effectively improved the quality of care for rectal cancer patients and increased the use of TME.[120,122]

The main limitation of all these studies is the lack of any quality of surgery data as volume can only ever be a proxy for experience, and whether or not this is a direct measure of surgical quality is not entirely clear. There is an argument for not adjusting for surgical technique as this is a measure of the surgeons experience and training[123] but the lack of data on this area is the real limitation. As volume is easily obtained it will likely remain the main estimate of surgical quality.

Chemotherapy

Chemotherapy improves prognosis and survival by decreasing tumour size before surgery and preventing metastases after surgery. Older colorectal patients were less likely to receive chemotherapy.[96,96,127] The proportion of older patients receiving chemotherapy improved in a study of colorectal cancer patients diagnosed during 1976 to 2003 Côte-d'Or region, France.[84]

Deprived patients are less likely to receive chemotherapy.[32,96,127] A population-based study of colorectal cancer patients in Yorkshire during 1986 to 1994 found patients were most likely to receive chemotherapy if their hospital of first admission provided chemotherapy.[32] However, no association was found after adjustment for stage.[32]

A population-based national study in Scotland between 1990 and 1994 of patients diagnosed under age 75 found patients aged 64 to 75 were most likely to receive chemotherapy compared with younger and older patients, although the extremely elderly (over 90) were the least likely to receive chemotherapy.[127] In a population-based study the age distribution for chemotherapy treatment was attributed to inadequate access to health care services and fitness for treatment associated with patients age at diagnosis.[127] However, stage at diagnosis was not included in the analysis so it is not possible to determine if lack of staging information or difference in stage at diagnosis played a roll in treatment provision.

Radiotherapy

Radiotherapy is effective at decreasing recurrence particularly for patients with rectal cancer in stages I or II at diagnosis.[121] Pre-operative radiotherapy is the recommended treatment for rectal cancer, decreasing the chance of local recurrence by up to 40%[85] and increasing survival at 5 years by 6% to 9%.[85,128] In England and Wales guidelines published in 1997 recommended radiotherapy is given with chemotherapy, as it makes the cancer more sensitive to radiotherapy.[42] Post-operative radiotherapy is generally limited to patients at high risk for recurrence[85] but has, as yet, not shown a survival or recurrence benefit. In a population-based cancer registry study of colorectal cancer in Yorkshire during 1986 to 1994 the proportion of rectal cancer patients treated with radiotherapy increased (8% during 1986-88 to 14% during 1992-94).[32] To my knowledge, there have been no further population-based survival analyses of radiotherapy treatment for UK colorectal cancer patients since the Yorkshire study. The Yorkshire study did not find socioeconomic variations in radiotherapy treatment but further population based studies are needed.

There is an inverse association between radiotherapy provision and age with patients over 85 least likely to receive radiotherapy.[129] In the US, ethnic differences have also been found with black patients receiving less radiotherapy than other ethnic groups.[129] In a US study of adjuvant therapy, physicians stated reasons for lack of chemotherapy

and radiotherapy provision were patient refusal (22% for radiotherapy), comorbidity, and lack of clinical indication were the main reasons.[129]

Future prevention

Screening

In the future, earlier diagnosis may be achieved through the national colorectal cancer screening programme in individuals aged 60 to 69 years old, which started in parts of the North West in September 2006 with national coverage by 2009. Screening for colorectal cancer can help to reduce mortality by identifying and treating cancers at earlier stage with deaths from colorectal cancer are estimated to drop by up to 16% in 60 to 69 year olds.[130] In the longer term incidence in the age group following the screening age, those aged over 70's, will decrease as tumours are detected while individuals are in their 60's by the screening programme.

Reducing inequalities

Clinical guidance in the National Health Service (NHS) aims to ensure effective and consistent treatment, standards and procedures across regions and services but is not mandatory. They can help to reduce variations across the health service that could contribute to inequalities. Guidance published in 1995, recommends a centralisation of cancer services resulting in more patients receiving treatment from specialist clinicians and treatment occurring at a cancer centre, which each have been shown to improve surgical outcomes and survival.[32,118,119,123] The national cancer plan (2000)[131] and the cancer reform strategy (2007)[132] provided further resources and centralisation of services, including the implementation of Multidisciplinary team meetings. Both of these plans aimed to decrease inequalities and improve cancer treatment and survival.

There is still regional variation but the implementation of guidance has improved outcomes for patients.[133,134] When interventions to improve population health are introduced, they improve health in all groups but larger improvements are usually seen in the affluent socioeconomic groups due to faster and higher take-up, resulting in a widening in inequalities.[135] Reducing inequalities may be achieved by targeting resources specifically at the deprived group to obtain improvements in the deprived faster than in the affluent.[135,136] To address this issue, the English government initiated a "Programme for Action" in 2003 which was a policy across many government departments aimed at tackling the poverty and causes of inequalities in health.[136] The

complexity of health inequalities required the government to address many issues not directly related to health, such as poverty, smoking cessation, early years support for families, poor housing and educational development. These interventions were not aimed specifically at cancer but should also decrease inequalities in cancer, although the impact may take many years with initial results indicating the programme has not yet improved the gap in life expectancy.[137] However, the target for decreasing mortality in the under 75s by 20% by 2010 will be reached.[137]

Inequalities have a substantial impact on mortality in colorectal cancer. An evaluation of the impact of inequalities estimated that by reducing rates of colorectal cancer in the deprived health authorities to the rates in the affluent health authorities 5,590 cases and 2,370 deaths per year could be avoided in the UK and Ireland.[138] This identifies an area where major improvements can be made by reducing risk factors, encouraging healthy lifestyles and ensuring equal access to health services in deprived socioeconomic groups.

An analysis of national cancer data in England in the 1990's quantified the impact improvements in cancer survival over time had on patients and found an increasing proportion achieved a normal life expectancy after diagnosis.[139] The largest improvements in survival occurred in cancers with newly introduced treatments, but these cancers accounted for relatively few incident cases.[139] For common cancers even small increases in survival had a large impact and resulted in substantial numbers of lives gained.[139] Improvements in survival between 1981-85 and 1986-90 in England and Wales resulted in 6% lower mortality (2,560 deaths) for colon cancer and4% lower mortality (1,090 deaths) for rectal cancer than would have been expected otherwise.[139] Most of the avoided deaths occurred in patients aged under 75.

Summary

Colorectal cancer survival has been improving but continues to be lower in the UK, particularly the North West, than the European average and in the USA. Most of the recent improvements in survival have been attributed to improvements in surgical technique and chemotherapy regimes. Survival is influenced by lifestyle factors, treatment and stage at diagnosis, all of which are known to vary by socioeconomic status. The cause of inequalities in colorectal cancer survival remains unclear with it attributed to variations in stage, comorbidity, type and quality of treatment. Generally

population-based studies are limited by missing data for stage, comorbidity and treatment, making plausible inferences difficult. In the following thesis I will evaluate the impact of comorbidity, clinical factors (including stage) and treatment have on the deprivation gap.

Reference List

(1) United States National Library of Medicine (NML). PubMed. 2006. (cited 10 Aug. 2006) Available from URL: www.ncbi.nml.nih.gov/PubMed

(2) Ovid Technologies Inc. EMBASE. 2006. (cited 10 Aug. 2006) Available from URL: http://gateway1.uk.ovid.com.ovidweb.cgi

(3) JISC, MIMAS, Thompson ISI. ISI web of knowledge service for UK education. 2006. (cited 10 Aug. 2006) Available from URL: http://wok.mimas.ac.uk

(4) Ovid Technologies Inc. WEBSPIRS 5.0 (SilverPlatter's Information Retrieval System for the World Wide Web). 2006. (cited 10 Aug. 2006) Available from URL: http://web5s.silverplatter.com/webspirs/start.ws

(5) The Cochrane Collaboration. The Cochrane Library. 2006. (cited 10 Aug. 2006) Available from URL: www.cochrane.org

(6) Google Inc. Google Scholar. 2005. (cited 10 Aug. 2006) Available from URL: http://scholar.google.com

(7) International Association for Research on Cancer (IARC). IARC publications list. 2006. (cited 10 Aug. 2006) Available from URL: www.iarc.com.fr/publica.htm

(8) Gatta G, Capocaccia R, Sant M, Bell J, Coebergh J, Damhuis RAM, Martines-Garcia C, Pawlega J, Ponz de Leon M, Pottier D et al. Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high-resolution study. *Gut.* 2000; 47:533-538.

(9) Boyle P, Langman JS. ABC of colorectal cancer: epidemiology. *British Medical Journal.* 2005; 321:805-808.

(10) Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. *Annals of Oncology.* 2006; 17:5-19.

(11) Sant M, Capocaccia R, Coleman MP, Berrino F, Gatta G, Micheli A, Verdecchia A, Faivre J, Hakulinen T, Coebergh JW et al. Cancer survival increases in Europe, but international differences remain wide. *European Journal of Cancer.* 2001; 37:1659-1667.

(12) Coleman MP, Babb P, Damiecki P, Grosclaude P, Honjo S, Jones J, Knerer G, Pitard A, Quinn M, Sloggett A, De Stavola B. *Cancer survival trends in England and Wales, 1971-1995: deprivation and NHS Region. (Studies in Medical and Population Subjects No. 61).* London: The Stationery Office, 1999.

(13) Coleman MP, Rachet B, Woods LM, Mitry E, Riga M, Cooper N, Quinn MJ, Brenner H, Estève J. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *British Journal of Cancer.* 2004; 90:1367-1373.

(14) ONS. Survival rates in England by SHA up to 2002. 2006. (cited 1 Sept. 2006) Available from URL: www.statistics.gov.uk

(15) Kogevinas M, Porta M. Socio-economic differences in cancer survival: a review of the evidence. In: Kogevinas M, Pearce N, Susser M, Boffetta P, editors. *Social Inequalities and Cancer. (IARC Scientific Publications No. 138).* Lyon: IARC, 1997, 177-206.

(16) Hole DJ, McArdle CS. Impact of socioeconomic deprivation on outcome after surgery for colorectal cancer. *British Journal of Surgery.* 2002; 89:586-590.

(17) Wrigley H, Roderick P, George S, Smith J, Mullee M, Goddard J. Inequalities in survival from colorectal cancer: a comparison of the impact of deprivation, treatment and host factors on observed and cause specific survival. *Journal of Epidemiology and Community Health.* 2005; 57:301-309.

(18) Polite BN, Dinham JJ, Olopade OI. Colorectal cancer model of health disparities: understanding mortality differences in minority populations. *Journal of Clinical Oncology.* 2006; 24:2179-2187.

(19) Whynes DK, Frew EJ, Manghan CM, Scholefield JH, Hardcastle JD. Colorectal cancer, screening and survival: the influence of socio-economic deprivation. *Public Health.* 2003; 117:389-395.

(20) Ward E, Jemal A, Cokkinides V, Singh GP, Cardines C, Ghafoor A, Thun M. Cancer disparities by race/ethnicity and socioeconomic status. *CA Cancer Journal for Clinicians.* 2004; 54:78-93.

(21) Prior P, Woodman CBJ, Collins S. International differences in survival from colon cancer: more effective care versus complete cancer registration. *British Journal of Surgery.* 1998; 85:101-104.

(22) Coleman MP, Gatta G, Verdecchia A, Estève J, Sant M, Storm H, Allemani C, Ciccolallo L, Santaquilani M, Berrino F et al. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. *Annals of Oncology.* 2003; 14:v128-v149.

(23) Coleman MP, Quaresma M, Berrino F, Lutz J-M, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T et al. Cancer survival in five continents: first world-wide comparison (CONCORD study). *Lancet Oncology.* 2008; 9:730-756.

(24) SEER. Introduction to colorectal cancer. 2006. (cited 11 Feb. 2006) Available from URL: http://training.seer.cancer.gov/ss_module04_colon/unit01_sec01_intro.html

(25) Du WB, Chia KS, Sankaranarayanan R, Sankila R, Seow A, Lee HP. Population-based survival analysis of colorectal cancer patients in Singapore, 1968-1992. *International Journal of Cancer.* 2002; 99:460-465.

(26) Faivre-Finn C, Bouvier-Benhamiche AM, Phelip JM, Manfredi S, Dancourt V, Faivre J. Colon cancer in France: evidence for improvement in management and survival. *Gut.* 2002; 51:60-64.

(27) McArdle CS, McKee RF, Finlay IG, Wotherspoon H, Hole DJ. Improvement in survival following surgery for colorectal cancer. *British Journal of Surgery.* 2005; 92:1013.

(28) Brewster DH, Thomson CS, Hole DJ, Black RJ, Stroner PL, Gillis CR. Relation between socioeconomic status and tumour stage in patients with breast, colorectal, ovarian and lung cancer: results from four national, population based studies. *British Medical Journal.* 2001; 322:830-831.

(29) Ionescu MV, Carey F, Tait IS, Steele RJC. Socioeconomic status and stage at presentation of colorectal cancer. *Lancet.* 1998; 352:1439.

(30) Woodman CBJ, Gibbs A, Scott N, Haboubi NY, Collins S. Are differences in stage at presentation a credible explanation for reported differences in the survival of patients with colorectal cancer in Europe? *British Journal of Cancer.* 2001; 85:787-790.

(31) Lyratzopoulos G, Sheridan GF, Michie HF, McElduff P, Hobbiss JH. Absence of socioeconomic variation in survival from colorectal cancer in patients receiving surgical treatment in one health district: cohort study. *Colorectal Disease.* 2004; 6:512-517.

(32) NYCRIS. *Cancer treatment policies & their effects on survival; colorectal.* Leeds: NYCRIS, 2000.

(33) Singh GK, Miller BA, Hankey BF, Edwards BK. *Area socioeconomic variations in the U.S.: cancer incidence, mortality, stage, treatment, and survival, 1975-1999.* Bethesda, MD: National Cancer Institute, 2003.

(34) Schrijvers C, Coebergh J, Mackenbach JP. Socioeconomic status and comorbidity among newly diagnosed cancer patients. *Cancer.* 1997; 80:1482-1488.

(35) Ciccolallo L, Capocaccia R, Coleman MP, Berrino F, Coebergh JWW, Damhuis RAM, Faivre J, Martinez-Garcia C, Møller H, Ponz de Leon M et al. Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. *Gut.* 2005; 54:268-273.

(36) SEER. Surveillance Epidemiology and End Results. 2006. (cited 1 Sept. 2006) Available from URL: http://seer.cancer.gov/

(37) Pollock A, Vickers N. Deprivation and emergency admissions for cancers of colorectum, lung, and breast in south east England: ecological study. *British Medical Journal.* 1998; 317:245-252.

(38) Schrijvers C, Mackenbach JP, Lutz J-M, Quinn M, Coleman MP. Deprivation, stage at diagnosis and cancer survival. *International Journal of Cancer.* 1995; 63:324-329.

(39) De Marco MF, Janssen-Heijnen MLG, van der Heijden LH, Coebergh JWW. Comorbidity and colorectal cancer according to subsite and stage: a population-based study. *European Journal of Cancer.* 2000; 36:95-99.

(40) Munro AJ, Bentley AHM. Deprivation, comorbidity and survival in a cohort of patients with colorectal cancer. *European Journal of Cancer Care.* 2004; 13:262.

(41) Adams J, White M, Forman D. Is the rate of biological ageing, as measured by age at diagnosis of cancer, socioeconomically patterned? *Journal of Epidemiology and Community Health.* 2005; 59:146-151.

(42) Department of Health. *Improving outcomes in colorectal cancer: the manual.* London: Department of Health, 1997.

(43) Association of Coloproctology of Great Britain and Ireland. *Guidelines for the management of colorectal cancer.* London: The Royal College of Surgeons of England, 2001.

(44) Pheby DFH, Levine DF, Pitcher RW, Shepard NA. Lymph node harvests directly influence the staging of colorectal cancer: evidence from a regional audit. *Journal of Clinical Pathology.* 2004; 57:43-47.

(45) Stocchi L, Nelson H, Sargent DJ, O'Connell D, Tepper JE, Krook JE, Bert R, and the North Central Cancer Treatment Group. Impact of surgical and pathological variables in rectal cancer: A United States community and cooperative group report. *Journal of Clinical Oncology.* 2001; 19:3895-3902.

(46) Adams J, White M, Forman D. Are there socioeconomic gradients in the quality of data held by registries? *Journal of Epidemiology and Community Health.* 2004; 58:1052-1053.

(47) Adams J, White M, Forman D. Are there socioeconomic gradients in stage and grade of breast cancer at diagnosis? Cross sectional analysis of UK cancer registry data. *British Medical Journal.* 2004; 329:142-143.

(48) Adams J, Audisio RA, White M, Forman D. Age-related variations in progression of cancer at diagnosis and completeness of cancer registry data. *Surgical Oncology.* 2005; 13:175-179.

(49) SEER. Anatomy of Colon and Rectum. 2006. Available from URL: http://training.seer.cancer.gov/ss_module04_colon/unit02_sec01_anatomy_fig02.html

(50) Merkel S, Mansmann U, Papadopoulos T, Wittekind C, Hohmberger W, Hermanek P. The prognostic inhomogeneity of colorectal carcinomas stage III. *Cancer.* 2001; 92:2754-2759.

(51) Astler VB, Coller FA. The prognostic significance of direct extension of carcinoma of the colon and rectum. *Annals of Surgery.* 1954; 139:846.

(52) Luke CG, Kuczwara B, Moore JE, Olver N, Penniment MG, Pittman K, Price TJ, Rieger NA, Roediger BWE, Wittchow DA et al. Treatment and survival from colorectal cancer: the experience of patients at South Australian teaching hospitals between 1980 and 2002. *Clinical Oncology.* 2005; 17:372-381.

(53) Heriot AG, Tekkis PP, Smith JJ, Cohen CRG, Montgomery A, Audisio RA, Thompson MR, Stamatakis JD. Prediction of postoperative mortality in elderly patients with colorectal cancer. *Diseases of the Colon and Rectum.* 2006; 49:1-9.

(54) Senior PA, Bhopal R. Ethnicity as a variable in epidemiological research. *British Medical Journal.* 1994; 309:327-330.

(55) Chien C, Morimoto LM, Tom J, Christopher IL. Differences in colorectal carcinoma stage and survival by race and ethnicity. *Cancer.* 2005; 104:629-639.

(56) Alexander D, Jhala N, Chatla C, Steinhauer J, Funkhouser E, Coffey CS, Grizzle WE, Manne U. High-grade tumour differentiation is an indicator of poor prognosis in African Americans with colonic adenocarcinomas. *Cancer.* 2005; 103:2163-2170.

(57) Stefanidis D, Pollock BH, Miranda J, Wong A, Sharkey FE, Rousseau DL, Thomas CR, Kahlenberg MS. Colorectal cancer in Hispanics: a population at risk for earlier onset, advanced disease, and decreased survival. *American Journal of Clinical Oncology.* 2006; 29:123-126.

(58) Govindarajan R, Shah R, Erkman LG, Hutchins LF. Racial differences in the outcome of patients with colorectal carcinoma. *Cancer.* 2003; 97:493-498.

(59) Bae SY, Choi SK, Kim KR, Park CS, Lee SK, Roh HK, Shin DW, Pie JE, Woo Zh, Kang JH. Effects of genetic polymorphisms of MDR1, FMO3, CYP1A2 on susceptibility to colorectal cancer in Koreans. *Cancer Science.* 2006; 97:774-779.

(60) Jeter JM, Kohlmann W, Gruber SB. Genetics of colorectal cancer. *Oncology.* 2006; 20:269-276.

(61) Brawley OW, Freeman HP. Race and Outcomes: Is this the end of the beginning for minority health research? *Journal of the National Cancer Institute.* 1999; 91:1908-1909.

(62) Bach PB, Schrag D, Brawley OW, Galaznik A, Yakren S, Begg CB. Survival of Blacks and Whites after a cancer diagnosis. *Journal of the American Medical Association.* 2004; 287:2106-2113.

(63) Schrijvers CT, Coebergh JW, van der Heijden LH, Mackenbach JP. Socioeconomic variation in cancer survival in the Southeastern Netherlands 1980-89. *Cancer.* 1995; 75:2946-2952.

(64) Stockton DL. Cancer survival in Scotland: Understanding social variations. PhD dissertation. London School of Hygiene and Tropical Medicine, London, 2001.

(65) Clinical Outcomes Working Group. *Clinical Outcome Indicators.* Edinburgh: Information and Statistics Division, 1995.

(66) Charlson ME, Pompei P, Ales K. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Disease.* 1987; 40:373-383.

(67) Southern DA, Quan H, Ghali WA. Comparison of the Elixhauser and Charlson/Deyo methods of comorbidity measurement in administrative data. *Medical Care.* 2004; 42:355-360.

(68) Ghali WA, Hall RE, Rosen AK. Searching for an improved clinical comorbidity index for use with ICD-9-CM administrative data. *Journal of Clincal Epidemiology.* 1996; 49:273-278.

(69) Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of Clincal Epidemiology.* 1992; 45:613-619.

(70) American society of anesthesiologists. ASA physical status classification system. 2008. (cited 7 Mar. 2008) Available from URL: www.asahq.org/clinical/physticalstatus

(71) Nuttal M, van der Meulen J, Emberton M. Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. *Journal of Clincal Epidemiology.* 2006; 59:265-273.

(72) Ouellette JR, Small DG, Termuhlen PM. Evaluation of Charlson-Age comorbidity index as predictor of morbidity and mortality in patients with colorectal carcinoma. *Journal of Gastroenterology and Surgery.* 2004; 8:1061-1067.

(73) Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care.* 2005; 43:1130-1140.

(74) Stukenborg GJ, Wagner DP, Connors AF. Comparison of the performance of two comorbidity measures, with and without information from prior hospitalizations. *Medical Care.* 2001; 39:727-739.

(75) Cleves MA, Sanchez N, Draheim M. Evaluation of two competing methods for calculating Charlson's comorbidity index when analyzing short-term mortality using administrative data. *Journal of Clinical Epidemiology.* 1997; 50:903-908.

(76) Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of Charlson comorbidity index predicted in-hospital mortality. *Journal of Clinical Epidemiology.* 2004; 57:1288-1294.

(77) Wood J, Hennell T, Jones A, Hooper J, Tocque K, Bellis MA. *Where wealth means health: Illustrating inequalities in the North West.* Liverpool: North West Public Health Observatory, 2006.

(78) Chan AO, Jim MH, Lam KF, Morris JS, Sui DC, Tong T, Ng FH, Wong SY, Hui WH, Chan CK et al. Prevalence of colorectal neoplasm among patients with newly diagnosed coronary artery disease. *Journal of the American Medical Association.* 2007; 298:1412-1419.

(79) Yancik R, Wesley MN, Ries LAG, Havlik RJ, Long S, Edwards BK, Yates JW. Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients. *Cancer.* 1998; 82:2123-2134.

(80) Gross CP, McAvay GJ, Krumholz HM, Paltiel AD, Bhasin D, Tinetti ME. The effect of age and chronic illness on life expectancy after a diagnosis of colorectal cancer: implications for screening. *Annals of Internal Medicine.* 2006; 145:646-654.

(81) Janssen-Heijnen MLG, Maas HA, Houterman S, Lemmons VEPP, Rutten HJT, Coebergh JW. Comorbidity in older surgical cancer patients: influence on patient care and outcome. *European Journal of Cancer.* 2007; 43:2179-2193.

(82) Kim YE, Gatrell AC, Francis BJ. The geography of survival after surgery for colorectal cancer in southern England. *Social Science and Medicine.* 2000; 50:1099-1107.

(83) Vercelli M, Lillini R, Capocaccia R, Micheli A, Coebergh J, Quinn M, Martinez-Garcia C, Quaglia A, The ELDCARE Working Group. Cancer survival in the elderly: Effects of socio-economic factors and health care system features (ELDCARE project). *European Journal of Cancer.* 2006; 42:234-242.

(84) Guyot F, Faivre J, Manifefi S, Meny B, Bonithon-Kopp C, Bouvier AM. Time trends in the treatment and survival from recurrence of colorectal cancer. *Annals of Oncology.* 2005; 16:756-761.

(85) Department of Health. *Guidance on commissioning cancer services: improving outcomes in colorectal cancer.* London: Department of Health, 1997.

(86) Expert Advisory Group on Cancer. *A policy framework for commissioning cancer services: a report by the Expert Advisory Group on cancer to the Chief Medical Officers of England and Wales.* London: Department of Health, 1995.

(87) Golfinopoulos V, Pentheroudakis G, Pavlidis N. Treatment of colorectal cancer in the elderly: a review of the literature. *Cancer Treatment Reviews.* 2006; 32:1-8.

(88) Bernardi D, Errante D, Galligioni E, Crivellari D, Bianco A, Salvagno L, Fentimann IS. Treatment of breast cancer in older women. *Acta Oncology.* 2008; 47:187-198.

(89) Neal RD, Allgar VL. Sociodemographic factors and delays in the diagnosis of six cancers: analysis of data from the *'National Survey of NHS Patients: Cancer'. British Journal of Cancer.* 2005; 92:1971-1975.

(90) Beaver K, Bogg J, Luker KA. Decision-making role preferences and information needs: a comparison of colorectal and breast cancer. *Health Expectations.* 1999; 2:266-276.

(91) Wichmann MW, Müller C, Hornung HM, Lau-Werner U, Schildberg FW, and the Colorectal Cancer Study Group. Gender differences in long-term survival of patients with colorectal cancer. *British Journal of Surgery.* 2001; 88:1092-1098.

(92) Wichmann MW, Ayala A, Chaudry IH. Male sex steroids are responsible for depressing macrophage immune function after trauma-hemorrhage. *American Journal of Physiology.* 1997; 273:13335-1340.

(93) Angele MK, Knöferl MW, Ayala A, Cioffi WG, Bland KI, Chaundry IH. Male and female sex steroids: do they produce deleterious or beneficial effects on immune responses after trauma and hemorrhage? *Surgical Forum.* 1998; 49:43-45.

(94) Wichmann MW, Zellwiger R, DeMaso CM, Ayala A, Chaudry IH. Enhanced immune responses in females, as opposed to decreased responses in males following haemorrhagic shock and resuscitation. *Cytokine.* 1996; 8:853-863.

(95) Wood J. *Rural health and health care: a North West perspective.* Lancaster: North West Public Health Observatory, 2006.

(96) Campbell NC, Elliot AM, Sharp L, Ritchie LD, Cassidy J, Little J. Impact of deprivation and rural residence on treatment of colorectal and lung cancer. *British Journal of Cancer.* 2002; 87:585-590.

(97) Campbell NC, Elliot AM, Sharp L, Ritchie LD, Cassidy J, Little J. Rural factors and survival from cancer: analysis of Scottish cancer registrations. *British Journal of Cancer.* 2000; 82:1863-1866.

(98) Campbell NC, Elliot AM, Sharp L, Ritchie LD, Cassidy J, Little J. Rural and urban differences in stage at diagnosis of colorectal and lung cancers. *British Journal of Cancer.* 2001; 84:914.

(99) Launoy G, Le Coutour X, Gignoux M, Pottier D, Dugleux G. Influence of rural environment on diagnosis, treatment, and prognosis of colorectal cancer. *Journal of Epidemiology and Community Health.* 1992; 46:365-367.

(100) Dray X, Boutron-Ruault MC, Bertrais S, Saphinho D, Benhamiche-Bouvier AM, Faivre J. Influence of dietary factors on colorectal cancer survival. *Gut.* 2003; 52:868-873.

(101) Woods LM, Rachet B, Riga M, Stone N, Shah A, Coleman MP. Geographic variation in life expectancy at birth in England and Wales is largely explained by deprivation. *Journal of Epidemiology and Community Health.* 2005; 59:115-120.

(102) Shohaimi S, Welch A, Bingham S, Luben R, Day NE, Wareham N, Khaw KT. Residential area deprivation predicts fruit and vegetable consumption independently of individual educational level and occupational social class: a cross sectional population

study in the Norfolk cohort of the European Prospective Investigation into Cancer (EPIC-Norfolk). *Journal of Epidemiology and Community Health.* 2004; 58:686-691.

(103) Drever F, Doran T, Whitehead M. Exploring the relation between class, gender, and self-rated general health using the new socioeconomic classification. A study using data from the 2001 census. *Journal of Epidemiology and Community Health.* 2004; 58:590-596.

(104) Dickman PW, Auvinen A, Voutilainen ET, Hakulinen T. Measuring social class differences in cancer patient survival: is it necessary to control for social class differences in general population mortality? A Finnish population-based study. *Journal of Epidemiology and Community Health.* 1998; 52:727-734.

(105) Carstairs V. Deprivation indices: their interpretation and use in relation to health. *Journal of Epidemiology and Community Health.* 1995; 49:s3-s8.

(106) Department of the Environment Transport and the Regions. *Measuring multiple deprivation at the small-area level: the Indices of Deprivation 2000.* London: DETR, 2000.

(107) Neighbourhood Renewal Unit, Office of the Deputy Prime Minister. *The English Indices of Deprivation 2004 (Revised).* London: ODPM, 2004.

(108) Jarman B. Identification of underprivileged areas. *British Medical Journal.* 1983; 286:1709.

(109) Townsend P, Phillimore P, Beattie A. Health and deprivation: inequality and the North. Bristol: Croom Helm; 1988.

(110) Woods LM, Rachet B, Coleman MP. Choice of geographic unit influences socioeconomic inequalities in breast cancer survival. *British Journal of Cancer.* 2005; 92:1279-1282.

(111) National Statistics. Health and Lifestyles Survey (HALS). 2006. (cited 7 Oct. 2006) Available from URL: www.statistics.gov.uk

(112) Institute for Social and Economic Research. British Household Panel Survey. 2006. (cited 7 Oct. 2006) Available from URL: www.iser.essex.ac.uk/ulsc/bhps

(113) Mohan J, Twigg L, Barnard S, Jones K. Social capital, geography and health: a small-area analysis for England. *Social Science & Medicine.* 2005; 60:1267-1283.

(114) Adams J, Ryan V, White M. How accurate are Townsend Deprivation Scores as predictors of self-reported health? A comparison with individual level data. *Journal of Public Health.* 2005; 27:101-106.

(115) Jordan CThomson C. *Comparison of incidence rates by deprivation quintile in breast, lung, cervix and melanoma cancer patients in England, 1998-2003.* Sheffield: Trent Cancer Registry, 2006.

(116) Jordan C, Palmater N, Thompson C. *Survival by deprivation in the Trent Strategic Health Authority Area - Comparison of Ward and SOA - level analysis.* Sheffield: Trent Cancer Registry, 2006.

(117) Yu XQ, O'Connell DL, Gibberd RW, Armstrong BK. A population-based study from New South Wales, Australia 1996-2001: area variation in survival from colorectal cancer. *European Journal of Cancer.* 2005; 41:2715-2721.

(118) Parry JM, Collins S, Mathers J, Scott NA, Woodman CBJ. Influence of volume of work on the outcome of treatment for patients with colorectal cancer. *British Journal of Surgery.* 1999; 86:475-481.

(119) Porter G, Soskolne C, Yakimets W, Newman S. Surgeon-related factors and outcome in rectal cancer. *Annals of Surgery.* 1998; 227:157-167.

(120) Kapiteijn E, Putter H, van de Velde CJH, and cooperative investigators of the Dutch ColoRectal Cancer Group. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in the Netherlands. *British Journal of Surgery.* 2002; 89:1142-1149.

(121) Manfredi S, Benhamiche AM, Meny B, Cheynel N, Rat P, Faivre J. Population-based study of factors influencing occurrence and prognosis of local recurrence after surgery for rectal cancer. *British Journal of Surgery.* 2001; 88:1221-1227.

(122) Mack LA, Temple Wj. Education is the key to quality of surgery for rectal cancer. *European Journal of Surgical Oncology.* 2005; 31:636-644.

(123) Renzulli P, Lowy A, Maibach R, Egeli RA, Metzger U, Laffer UT. The influence of the surgeon's and the hospital's caseload on survival and local recurrence after colorectal cancer surgery. *Journal of Surgery.* 2006; 139:296-304.

(124) Duxbury MS, Brodribb AJ, Oppong FC, Hosie KB. Management of colorectal cancer: variations in practice in one hospital. *European Journal of Surgical Oncology.* 2003; 29:400-402.

(125) Jestin P, Påhlman L, Glimelius B, Gunnarsson U. Cancer staging and survival in colon cancer is dependent on the quality of the pathologists' specimen examination. *European Journal of Cancer.* 2005; 41:2071-2078.

(126) Blomqvist P, Ekbom A, Nyrén O, Krusemo UB, Bergström R, Adami HO. Survival after rectal cancer: differences between hospital catchment areas. A nationwide study in Sweden. *Gut.* 1999; 45:39-44.

(127) McLeod A. Variation in provision of chemotherapy for colorectal cancer. *Journal of Epidemiology and Community Health.* 1999; 53:775-781.

(128) Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *The New England Journal of Medicine.* 1997; 336:980-987.

(129) Ayanian JZ, Zaslavsky AM, Fuchs CS, Guadagnoli E, Creech CM, Cress RD, O'Connor LC, West DW, Allen ME, Wolf RE et al. Use of adjuvant chemotherapy and radiation therapy for colorectal cancer in a population-based cohort. *Journal of Clinical Oncology.* 2003; 21:1293-1300.

(130) UK Colorectal Cancer Screening Pilot Group. Results of the first round of demonstration pilot of screening from colorectal cancer in the United Kingdom. *British Medical Journal.* 2004; 329:133-135.

(131) Department of Health. *The NHS Cancer Plan.* London: Department of Health, 2000.

(132) Department of Health. *Cancer Reform Strategy.* London: Department of Health, 2007.

(133) Haward RA. The Calman-Hine report: a personal retrospective on the UK's first comprehensive policy on cancer services. *Lancet Oncology.* 2006; 7:336-346.

(134) Morris E, Haward RA, Gilthorpe MS, Craigs C, Forman D. The impact of the Calman-Hine report on the process and outcomes of care for Yorkshire colorectal cancer patients. *British Journal of Cancer.* 2006; 95:979-985.

(135) Crombie IK, Irvine L, Elliot L, Wallace H. *Policies to reduce inequalities in health in 13 developed countries.* Edinburgh: NHS Health Scotland, 2005.

(136) Department of Health. *Tackling health inequalities; a programme for action.* London: Department of Health, 2003.

(137) Department of Health. *Tackling Health Inequalities: Status Report on the Programme for Action.* London: Department of Health, 2005.

(138) Quinn MJ, Wood H, Cooper N, Rowan S. *Cancer atlas of the United Kingdom and Ireland 1991-2000. (Studies on Medical and Population subjects No. 68).* London: The Stationery Office, 2005.

(139) Richards MA, Stockton D, Babb P, Coleman MP. How many deaths have been avoided through improvements in cancer survival? *British Medical Journal.* 2000; 320:895-898.

Chapter 3

Materials and data

Overview

Data from population-based cancer registries are ideal for analysing incidence and survival but they are known to have incomplete treatment details and do not normally record details of comorbid conditions. By contrast, routine hospital discharge records, which are collected to evaluate activity for payment, provide in principle a complete record of treatment and comorbidity that can be used in population-based epidemiological studies. For this thesis, demographic and tumour details will be taken from cancer registry data. Cancer registry data will be linked to Hospital Episode Statistics (HES) to augment the treatment details, thereby improving the completeness of surgical details. Only 67% of patients were recorded as having surgery in cancer registry data but this increased to 82% after information from HES was also used. For each colorectal patient recorded at the cancer registry information on comorbidity, or previous illnesses, will be obtained from HES for previous hospital admissions. This chapter describes the type of data collected by both cancer registries and HES, and the methods of data management and linkage, and the creation and definition of new variables to create the analytical dataset.

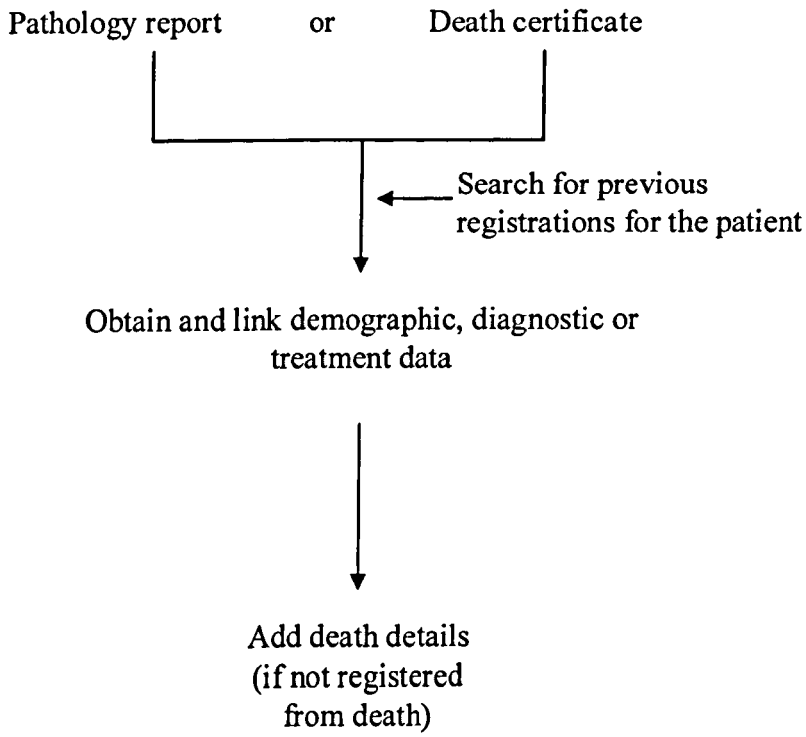
Cancer Registry data

Data collection

Cancer registries collect information on cancer diagnosis, treatment and demographics (Appendix 3.1) to a consistent national standard.[1] Initial notification of tumours occurs through the provision of pathology, cytology, haematology, hospital records or death records. (Figure 3.1). After initial notification, hospital records, general practitioners and other sources are checked for information on treatment and stage. Other registries will provide details of a North West resident diagnosed or treated in their region.

In the UK, death details for cancer patients, necessary to analyse survival, are relatively complete. The National Strategic Tracing Service (NSTS) provides death details to the cancer registry for patients registered with cancer and individuals with cancer mentioned on the death certificate. NSTS also provides missing core patient demographic details such as gender, name, address, date of birth for cancer registrations.

Figure 3.1: Cancer registration pathways



Merseyside and Cheshire Cancer Registry (MCCR) and North West Cancer Registry (NWCR) both collect information in a broadly similar manner, although there are some

differences in the collection of treatment and stage data. In MCCR, during the period covered by this research cancer (1997-2004) registration officers collected treatment and staging information mainly from case-notes or electronic hospital records (mainly from the specialist cancer centre). At NWCR clinical coders in each hospital complete a registration cancer registry form providing demographic, personal, diagnostic and treatment details. In order to ensure accurate coding by hospital staff, a NWCR Quality Assurance officer regularly visits hospitals to train hospital clinical coders and audit case-notes.

MCCR recorded registrations on a person- and tumour-based system providing an internal linkage for patients with multiple tumours. The NWCR database was only tumour-based. Since 2006, treatment and staging information has been collected electronically from hospital trusts.

Data

Data were extracted from NWCR (28/09/2006) and MCCR (10/02/2007) for all resident colorectal cancer patients (ICD-10 C18-C20) diagnosed between 1997 and 2004 in separate linkable files for tumour, treatment and stage details (3 for NWCR, 3 for MCCR) (Appendix 3.1). The tumour and treatment data were managed separately until the final step because the treatment data was episode-based (i.e. containing a separate row for each treatment episode), rather than tumour-based (i.e. one record for each tumour).

Demographic details

Demographic information, such as name, address and date of birth, is obtained from pathology reports and confirmed by the tracing service (Appendix 3.1). Pathology reports do not record NHS number but this is obtained from the tracing service or other hospital records.

Tumour details

Each Cancer registration record contains the specific tumour details of cancer site, histology, stage, grade and date of diagnosis for every incident case. Colorectal cancer is normally confirmed pathologically, enabling the specific histological type of tumour to be determined, by microscopic verification (MV). Colorectal cancer confirmed by cytology was also considered microscopically verified, although this is uncommon for

colorectal tumours. Histology is recorded as a five digit number using the International Classification of Diseases for Oncology 2nd edition (ICD-O2) morphology coding system.[2] The final digit denotes the tumour behaviour (e.g. invasive, benign). When multiple pathology information is received for the same colorectal cancer (i.e. the patient has more than one operation) the most recent or specific is used. Histology can be non-specific (e.g. neoplasm, not otherwise specified) or specific (e.g. mucinous or serous). Non-specific coding occurs when pathology is unavailable or insufficient to determine specific histology.

The most accurate method of staging is through a combination of pathological assessment of tumour tissue and of the associated lymph nodes. In order to fully assess stage it is necessary to comprehensively sample at least 12 lymph nodes during surgery.[3] Cancer registries record stage at diagnosis from pathology records, clinical diagnosis and other sources (case-notes or electronic hospital records).

Treatment

Cancer registries record the date of treatment, type of procedure, surgeon and hospital for any surgery, chemotherapy or radiotherapy treatment within 6 months of diagnosis. For chemotherapy and radiotherapy, only the first instance is recorded. Surgery type was coded to the Office of Population, Census, and Surveys: Classification of Interventions and Procedures, 4th Revision (OPCS-4). Treating surgeon was recorded as the General Medical Council code for MCCR and HES. NWCR records the treating surgeon in free text, so for surgeon volume analysis, HES data will be substituted.

Dataset cleaning

All adults aged 15-99 years diagnosed with a first primary invasive, malignant colorectal cancer (ICD-10 C18-C20) between 1997 and 2004 who were resident in the North West of England and registered in the North West Cancer Intelligence Service were eligible for analysis. The dataset was then checked for incorrect or rare coding combinations, further checks of age and dates were conducted before excluding ineligible patients.

Quality assurance

All tumours were checked for correct morphology and site combinations using the International Agency for Cancer Research checking programme (IACR tools v2.0 IARC),[4] a widely used tool for quality assuring cancer registry data. There were seven tumours (0.02%) identified with a rare morphology (malignant melanoma NOS, mixed malignant tumour and malignant teratoma) [h] but after case-note review were found to be correct. IARC checks were routinely used (normally every quarter) to quality assure the data, so the low proportion of errors was expected. Only 33 patients were under the age of 19 (0.1%) at diagnosis. For these patients, registry notes were reviewed by a registration officer and no errors were found.

NHS number was missing for some patients diagnosed during the 1990s (124 cases from MCCR, 852 cases from NWCR). National Strategic Tracing Service was used to obtain NHS number for these patients but 55 (0.2%) remained missing (42 cases from MCCR, 13 cases for NWCR).

Exclusions

Of the 30,656 eligible patients, 1,799 cases (or 6% of cases) were excluded because they were outside of age limits (<15 or >99), death certificate only (DCO) or a second primary (Table 3.1). The remaining dataset included 29,563 patients who were linked to data for HES to provide additional clinical information. There were no significant differences in the probability of exclusions between NWCR and MCCR.

Table 3.1: Exclusions by registry

	MCCR				NWCR				Combined		
			95% CI				95% CI				Significant
Exclusions	No.	%	lower	upper	No.	%	lower	upper	No.	%	(p<0.05)
Age <15 or >99	3	<0.1	0	1.8	19	0.1	0	1.5	22	0.1	
Death certificate only	543	4.5	2.8	6.3	328	1.7	0.3	3.1	871	2.8	
Multiple primary	229	1.9	0.1	3.7	677	3.5	2.1	4.8	906	2.9	
Zero survivor*	561	4.7	2.9	6.4	673	3.4	2.1	4.8	1234	3.9	

*Zero survors wil be included in the analysis with survival converted to one day

Registrations where the only record of a cancer diagnosis is the date of death (death certificate only, DCO), were excluded from the analysis because the 'true' date of diagnosis and thus the survival time was not known. The proportion of DCO registrations was very low and was not significantly different between MCCR and

[h] Corresponding ICD-O-2 morphology codes are 87203, 89403 and 90803, respectively

NWCR or socioeconomic groups. When the first record of a patient's diagnosis or treatment was the same as the date of death, known as zero survivors, survival time was converted to one day to include them in the analysis. Zero survivors include patients presenting late (usually as an emergency) and dying in their first diagnostic or treatment episode (e.g. surgery) or patients in whom a diagnosis had been made earlier but was not recorded at the registry. The proportion of zero survivors was non-significantly higher in MCCR than NWCR because NWCR will record previous treatment without a treatment date thereby decreasing the number of zero survivors.

Only the first primary colorectal cancers were included because the treatment and outcome of any subsequent primary colorectal tumour would be influenced by the first colorectal cancer. MCCR had lower levels of multiple tumours than NWCR (although non-significant) because the data base was both person- and tumour-based making checks for previous (and subsequent) cancers more complete.

Both HES and registry dates are internally quality assured for consistency of dates (e.g. no treatment after death, death before birth etc.). Additional checks did not find any discrepancies.

Hospital Episode Statistics

Data collection

The Hospital Episode Statistics (HES) records include all inpatient admissions occurring since 1989 and all outpatient admissions since 2002 for all NHS patients. The HES dataset includes demographic, clinical, administrative and geographic information. Information is recorded as a Finished Consultant Episode, which is a period of admitted patient care under a particular consultant or allied healthcare professional. Episodes begin at hospital admission or when the patient is transferred from another specialty (e.g. patient transferred from geriatrics to medical oncology). Diagnoses were coded according to the International Classification of Diseases, 10th Revision (ICD-10) and procedures coded to (OPCS-4).

The HES database includes seven diagnosis fields (DIAG_01 to DIAG_07) and four operative procedure fields (OPERTN_01 to OPERTN_04) until 2002 after which it was extended to 14 diagnosis fields and 12 operative fields.

Data quality

HES data are cleaned, validated and quality assured annually by the NHS Information Centre, which manages the dataset,[5] but there have been very few external assessments of HES accuracy and completeness. A study on the accuracy and completeness of death details for congenital heart surgery was critical of the completeness at some hospitals.[6] For this thesis, death details will be used from cancer registry data and cancer registry treatment will be combined with HES data on treatment.

Data

HES data for all cancer patient admissions in the North West between 1996/97 and 2004/05 were received from the Information Centre[7] (06/12/2006) in 21 pipe delimited ASCII files (Table 3.2). A further extract for 2005/06 was obtained from the National Cancer Action Team (NATCATSAT), because the processing time for the Information Centre procedures meant the most recently available year (at that time) could not be included. Obtaining the HES data from 1996/97 was chosen because of recording changes (from ICD-9 to ICD-10), health service geography changes (District Health Authorities to Primary Care Trusts) and improvements in data completeness. Stat Transfer[8] was used to convert files from ASCII into STATA format.

Table 3.2: HES data files

Cancer admissions		Non-cancer admissions	
Financial year	No. of records	Financial year	No. of records
2005/06*	219,194	2005/06*	646,302
2004/05	169,462	2004/05	324,854
2003/04	177,337	2003/04	345,187
2002/03	185,471	2002/03	353,363
2001/02	189,701	2001/02	363,932
2000/01	224,838	2000/01	410,498
1999/00	264,788	1999/00	447,864
1998/99	247,639	1998/99	421,369
1997/98	223,738	1998/97	377,462
1996/97	166,006	-	

*Includes patients treated in but resident outside the North West

Demographic and patient details

Patients are uniquely identified by the HES patient identifier which is generated by internally matching records for the same patient using NHS number, hospital case number, postcode, sex and date of birth for the entire HES dataset (Table 3.3). Each discharge episode is also uniquely identified by an episode key. Demographic variables were confirmed with the National Strategic Tracing Service.

Table 3.3: HES demographic variables

Name	HES field names	Format	Description
HES identifier	Hesid	10 digit numeric	Unique patient identifier
Episode key	Epikey	8 digit numeric	Episode identifier
Sex*	Sex	1 = men, 2= women	Gender
NHS number*	Newnhsno	10 digit numeric	NHS
Postcode*	Homeadd	7 digit alpha-numeric (e.g. CW9 6EL)	Postcode of residence
Date of birth*	dob	dd/mm/yyyy	Date of birth

*used for probability linkage to cancer registry data

Clinical and administrative

Dates of admission and discharge were recorded along with surgery dates (Opdate_01 to Opdate_12), with the order corresponding to the operation order and code (Oper_01 to Oper_12) (Table 3.4). Procedure codes are recorded in decreasing importance with the main surgery first (Oper_01). Health geography codes for the treatment provider including hospital, primary care trust, health authority and government office region are recorded using the National Administrative Codes Service coding system. The national General Medical Council registration number is recorded for the treating surgeon, although this is not always complete.

Table 3.4: HES clinical and administrative variables

Name	HES field names	Format	Description
Date of admission	ADMINDATE	dd/mm/yyyy	Date of admission (or transfer into specialty)
Diagnosis	DIAG_01 to _12	ICD-10	Diagnosis for which the patient is undergoing treatment
Operation (1 to 12)	OPER_01 to _12	OPCS-4 coding	Surgical procedure
Date of Operation	OPDATE_01 to _14	dd/mm/yyyy	Date of procedure (corresponds to procedure above)
Consultant	CONSULT	7 digit	National unique General Medical Council clinician
Date of discharge	DISDATE	dd/mm/yyyy	Date of discharge or transfer of care to another clinician
Hopital of admission	PROCODE	5 digit	National hospital code (5 digit)
Hopital of admission	PROCODE3/T	3 digit	National hospital code (3 digit)
Primary Care Trust of admission	PCTTREAT	3 digit	Primary care trust of treatment

Data management

Probability matching

Probability matching was conducted rather than one-to-one matching by NHS number, because some patients had incomplete demographic information; a significant problem in HES. Linkage of HES to cancer registry data was done by probability matching of date of birth, NHS number, sex and postcode. Preference for linkage was given to pairs of records with the most matches in the sequential hierarchy such as patients matching on more than one of NHS number, date of birth, postcode and sex, rather than a single match (e.g. NHS number) (Table 3.5). Each hospital attendance (from HES) was linked to the most complete match (lowest ranking). Only HES records that matched to the cancer registry and had a mention of colorectal cancer in DIAG_01 to DIAG_14 were assumed to be colorectal cancer treatment.

Table 3.5: HES and cancer registry matching

	1	2	3	4	MCCR (n=11,962)		NWCR (n=19,622)	
Hierarchy	NHS number	Date of Birth	Postcode	Sex	Tumour matches	%	Tumour matches	%
1	✓	✓	✓	✓	7,281	60.9	13,194	67.2
2	✓	✓	✓		50	0.4	103	0.5
3	✓	✓		✓	995	8.3	1,397	7.1
4	✓		✓	✓	159	1.3	267	1.4
5	✓	✓			32	0.3	41	0.2
6	✓		✓		4	<0.1	9	<0.1
7	✓			✓	37	0.3	54	0.3
8	✓				6	0.1	7	<0.1
9		✓	✓	✓	955	8	1,238	6.3
10		✓	✓		10	0.1	18	0.1
Unmatched					**2,433**	**20.3**	**3,294**	**16.8**
Total matched					**9,529**	**79.7**	**16,328**	**83.2**

The linkage between HES and cancer registry data was very good with over 80% matching and the majority of cases (67% in NWCR, 61% in MCCR) matching completely (NHS number, date of birth, postcode and sex). Those matching on hierarchy numbers 8 to 10 were more common in the earlier years, when HES and cancer registry recording was less accurate. For some patients an admission prior to diagnosis occurred, however these were mostly less than ideal matches (8 to 10). A small number of patients had a hospital admission with no OPCS-4 code recorded for any treatment procedure (4%, n=1,262).

Audit of linkage quality

The HES-to-registry linkage quality was consistent with a separate linkage in Northern and Yorkshire Cancer Registry and Intelligence Service (NYCRIS) national colorectal audit (Table 3.6). The NYCRIS colorectal audit linked cancer registry and HES data for the same time period (1997-2004) but the NYCRIS data was extracted at different times. The NYCRIS audit aimed to evaluate rectal cancer patients receiving surgery, with surgery data solely obtained from HES.[9] Despite a similar linkage method for both the audit and this study differences would be expected because i) of the probabilistic nature of the linkage and ii) differences in the registry and HES datasets (different extraction dates).

Direct comparison between the NYCRIS audit and this analysis found the linkage quality was high and corresponded well. The majority of patients matched to HES were linked to the same patient HESID[i] (n=22,910 or 78.0%) or had no HES admission (2,964, 10.1%) in both analyses. There were 172 more patients in this cancer registry dataset than the NYCRIS dataset because this data was extracted at a later date and included additional registrations (or patients where an earlier diagnosis data or treatment shifted the diagnosis date). The main difference between the NYCRIS linkage and this linkage was the HES dataset used in the NYCRIS linkage included all hospital admissions, regardless of whether cancer was mentioned. This resulted in an additional 10% of patients being linked, although most of the hospital admissions will be for non-colorectal cancer treatment. For these patients the HESIDs obtained from the NYCRIS linkage were used to obtain previous surgery and comorbidity for these patients. The miss-match rate was very low; only 1.3% of patients had a different HESID assigned in NYCRIS and this analysis.

[i] HESID is a unique number assigned to each patient in HES. HESID enables analysis across patient pathways over many years or across different hospitals, without the use of identifiable information (e.g. NHS number).

Table 3.6: Comparison of HES linkage for NYCRIS Colorectal audit and NW Colorectal survival project (cases in both data sets N=29,391)

Comparison	Comment/reason	No.	%
Same HESID	Exact match	22,910	78.0
NYCRIS missing HESID (but in NW)	NW data extracted later, patient recently added	75	0.3
NW missing HESID (but in NYCRIS)	NYCRIS linked to all hospital admissions (NW liked to admissiong with a mention of cancer)	3,074	10.5
Both missing HESID	Patient not admitted to hospital or not recorded/incomplete demographic data	2,964	10.1
NW and NYCRIS have different HESID	Differences due to chance (probablility matching)	368	1.3

Every effort was made to audit this dataset against the National Bowel Cancer Audit Programme (NBOCAP), however the NBOCAP audit did not have complete coverage of the North West and it was not possible to obtain individual level data.[10]

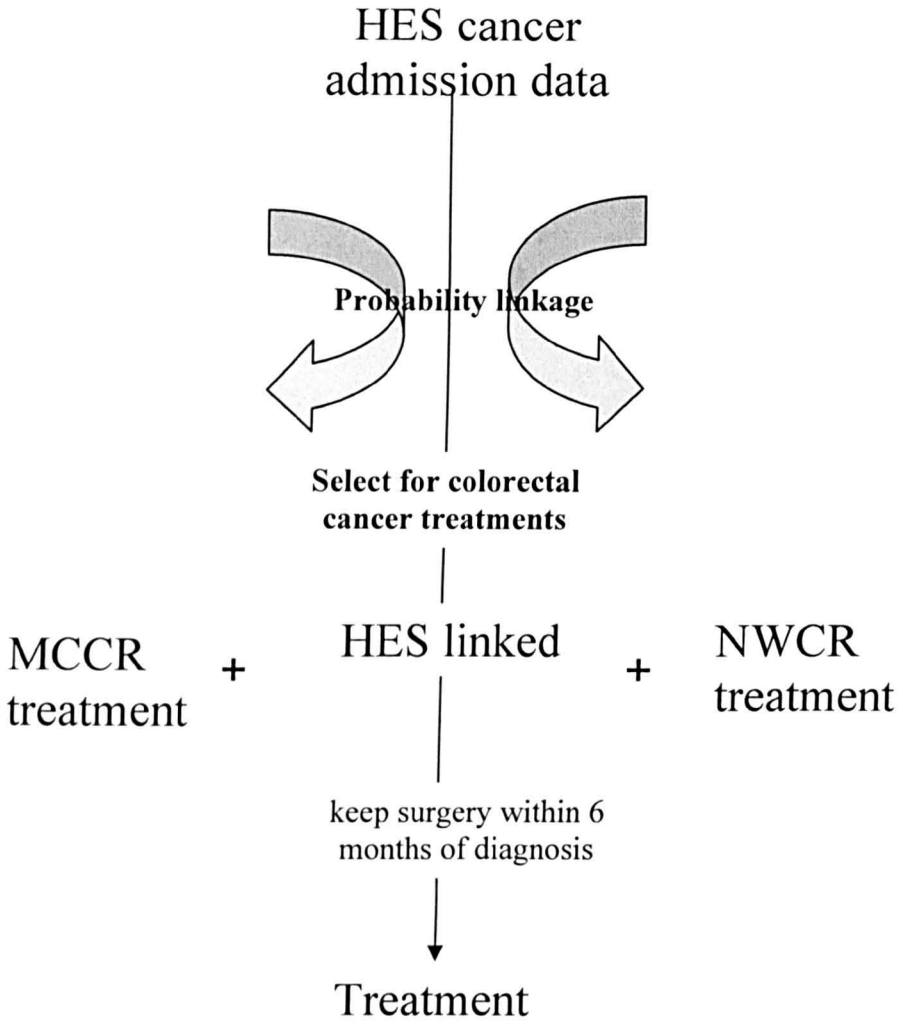
Surgery

Before matching HES data to cancer registry treatment data there were a number of data management steps to prepare both datasets. First, the HES data were linked to cancer registry patients providing a cancer registry tumour number for later links. All surgery details from HES were limited to the 6 months after diagnosis to be consistent with the registry data. The surgery file containing registry and HES procedures was sorted by treatment date and reformatted into a wide file format (surgery_n, surgeon_n, treathosp_n, surg_code_n) and limited to the first six colorectal surgical procedures (Figure 3.2). Colorectal surgical procedures were limited to six for practicality and because they included all excision or colorectal cancer procedures. Only surgical procedures related to colorectal cancer treatment were retained. The relevant codes were identified through advice from clinicians and registry clinical coders. The selected colorectal procedure codes were intentionally broad to ensure procedures with a non-specific coding were included (e.g. excision of stomach, large intestine, liver for metastasis, or abdomen NOS) (Appendix 3.2). All such surgery codes occurring in any of the first six diagnostic procedure codes in HES were included. After linkage, 82% of patients were found to have had at least one surgical procedure.

Lastly, the formatted HES data were linked to registry treatment data using the cancer registry tumour number and date of treatment (with a 3-day variance of date allowed). Linkage between a cancer registry surgery and HES surgery information was in agreement for the majority of dates but there was less agreement for procedure codes, although there was usually greater specificity in HES. Surgery dates for the same

procedures differed between registry and HES records by up to 3 days. This was due to the difference between procedure and pathology date, with the latter up to 3 days later. In cancer registries, the pathology date is used for case registration and surgical date. Only 22% of the operations recorded on MCCR had coding exactly matching those recorded in HES, with the majority of these (85%) also matching for date, or within 3 days (10%). The number of matching procedure codes is likely to be low, as HES includes data on many associated procedures (e.g. sampling of lymph nodes, opening of chest cavity), while registry records contain only the main surgery (excision). For procedures occurring on the same day in both HES and cancer registry data for which the OPCS-4 surgery codes did not agree HES was taken as more accurate because a) hospital clinical coders have access to full notes and electronic hospital files b) it is consistent and robust across hospital trusts and time.

Figure 3.2: Treatment file management



Chemotherapy data

HES admissions with a record of 'Continuous infusion of therapeutic subs' (OPCS-4 X35) or 'Other intravenous injection' (OPCS-4 X29) within 6 months of diagnosis were considered to be chemotherapy treatment and were combined in the HES data. Unfortunately, HES is known to under record chemotherapy, both for X35 and X29. Additionally, HES will have no record of chemotherapy received orally. Chemotherapy regime was not recorded in either data sources. Chemotherapy receipt from HES was combined with chemotherapy treatment from the cancer registry to provide a record of chemotherapy receipt (Yes/No/missing). Chemotherapy data in both HES and cancer registry data was known to be incomplete; therefore missing chemotherapy was imputed to take into account missing data.

Radiotherapy

Radiotherapy treatment was only recorded in cancer registration data but has high levels of completeness. Radiotherapy treatment occurs only at three specialist treatment centres in the North West (Christie Hospital; Manchester, Clatterbridge Centre for Oncology; Wirral and Rosemere Cancer Unit; Preston) which provide treatment data directly to the registries. The presence or absence of radiotherapy treatment within six months of diagnosis was taken from the cancer registry dataset.

Creating and defining variables

Demographic, diagnostic and radiotherapy details were obtained from the cancer registry database (Appendix 3.1). Surgical and chemotherapy details were obtained from both cancer registry data and HES.

Survival time and censoring

Survival time is the time from diagnosis to death or loss to follow-up. Follow-up data was obtained for all patients up to 31 December 2007. Patients still alive at 31 December 2007 were censored on that date.

Age

Age at diagnosis was calculated from the dates of birth and diagnosis, which are available for all cases (Table 3.7). Patients were grouped into 10-year age groups with the exception of patients aged 15 to 44, and those over 85. Patients aged under 15 and over 99 at diagnosis (n=22) were excluded from the analysis because they were childhood cancers and the life tables are only available up to age 99.

Table 3.7: Age grouping

Age at diagnosis	No.	%
15 to 44	757	2.6
45 to 54	2,107	7.1
55 to 64	5,531	18.7
65 to 74	9,224	31.2
75 to 84	8,926	30.2
85 to 99	3,018	10.2
Total	**29,563**	**100.0**

Site

Cancer site (topography) was recorded in the International Classification of Diseases for Oncology 2nd edition (ICD-O-2) coding system. The International Classification of

Diseases version 10 (ICD-10) coding system is normally used for cancer epidemiology and incorporates both tumour site and histology. ICD-O-2 codes (site and histology combinations) were converted to ICD-10 using the IARC conversion program.

Colon cancers can be further stratified into the 10 sub-sites based on the 4-digit ICD-10 code, while rectosigmoid (C19) and rectum (C20) are not subdivided under ICD-10 coding (Table 3.8). The majority of the analysis was based on colorectal cancers (combined) but where there are substantial differences, such as treatment, colon and rectal (including rectosigmoid) was analysed individually.

Most colorectal cancer cases were colon (61.6%) or rectal cancer (30.3%). Rectosigmoid cancers only accounted for 8.1%. Within the colon, cancers were most likely to be located in the caecum (12.8%), sigmoid (19.3%) or unspecified site (13.9%).

Table 3.8: Description of colorectal sub-sites and ICD-10 coding

Cancer site	Sub-site	No.	%
Colon (C18)		18,221	61.6
C18.0	Caecum	3,780	12.8
C18.1	Appendix	202	0.7
C18.2	Ascending colon	1,322	4.5
C18.3	Hepatic flexure	458	1.6
C18.4	Transverse colon	1,123	3.8
C18.5	Splenic flexure	512	1.7
C18.6	Descending colon	721	2.4
C18.7	Sigmoid colon	5,701	19.3
C18.8	Overlapping lesion of colon	303	1.0
C18.9	unspecified subsite	4,099	13.9
Rectosigmoid (C19)		2,400	8.1
Rectum (C20)		8,942	30.3
Total		**29,563**	**100.0**

Date of diagnosis

Date of diagnosis was taken from cancer registry data because cancer registries have strict criteria for registering a definitive cancer diagnosis[11] and HES records may include a presumptive diagnosis. For patients diagnosed by microscopic verification, date of diagnosis is the first date of pathology or treatment (whichever is first). The incidence date for patients diagnosed without pathology is the earliest of the following dates:

- first hospital attendance
- if no hospital attendance, he date of diagnosis at GP
- if no GP record of colorectal cancer or hospital attendance, the date of death

Grade

Grade is a measure of the level of cell differentiation as determined at pathology. Grade was obtained from the cancer registry data via pathology reports. Grade I tumours are well differentiated, or low grade, and progress to grade IV, or undifferentiated (Table 3.9). Tumours in the higher grades have generally been developing for a long time or are aggressive tumours and have a poorer prognosis.[12]

Table 3.9: Tumour grade

Description	No.	%
I	3,212	10.9
II	16,047	54.3
III	2,845	9.6
IV	62	0.2
unknown	7,397	25.0
Total	**29,563**	**100.0**

Stage

Stage at diagnosis was recorded in cancer registry data in various formats, including TNM, Dukes'[13] and Astler-Collier,[14] also known as amended Dukes' stage. These three coding systems convert to the widely used summary stages I to IV (Table 3.10).

Table 3.10: Staging for colorectal cancer in TNM and Dukes'

Summary stage	TNM stage	Primary tumour	Regional node involvement	Distant metastasis	Dukes' stage	Astler-Collier
-	0	*in situ*	N0	M0	-	-
I	I	T1	N0	M0	A	A
		T2	N0	M0	A	A
II	IIA	T3	N0	M0	B	B1
	IIB	T4	N0	M0	B	B2
	IIIA	T1-T2	N1	M0	C	C1
III	IIIB	T3-T4	N1	M0	C	C2
	IIIC	Any T	N2	M0	C	C2
IV	IV	Any T	Any N	M1	D	D
unknown						

Stage at diagnosis was recorded in summary stage in NWCR data, however MCCR data included all constituent parts to determine stage for many patients (Tumour, Nodes, Metastasis). Clinical coders at NWCR assessed the stage data assigning the appropriate stage; if the data was not complete they would assess all information available

(including treatment) and assign the appropriate stage based on TNM-5 coding rules. MCCR record stage (TNM, Dukes) and constituent parts (Tumour, Nodes, Metastasis) which was used to determine summary stage as defined in the algorithm in Table 3.10. Stage was available for 60.5% of patients, which is consistent with completeness of other UK registries (Table 3.11).[15] Stage was imputed using ICE multiple imputation methods[16] in STATA 10.0.[17]

Table 3.11: Distribution of stage at diagnosis

Stage at diagnosis	No.	%
I	2,191	7.4
II	7,322	24.8
III	7,722	26.1
IV	644	2.2
Not known	11,684	39.5
Total	**29,563**	**100.0**

Population-based cancer registry datasets have high levels of completeness for many variables, but obtaining complete data on stage remains a challenge. For colorectal cancer patients diagnosed in 2003, stage was recorded for 62% in MCCR, 56% in NWCR and 75% in Scotland (2002) compared to a UK average of 64%.[15] Registrations with an unknown stage fall into one of three groups.[18]

a) Staged, but adequate complete information not available (e.g. missing pathology report)

b) Stage could not be determined with the investigations undertaken (e.g. pathological sample insufficient)

c) Investigations were not carried out (e.g. not relevant for palliative care)

Patients with late stage tumours may be more likely to have missing data, as staging information may not be clinically relevant for patients receiving palliative care. Stage at diagnosis may also be associated with other prognostic factors, including age,[19] socioeconomic status,[20,21] sub-site, and treatment. Patients with missing data for stage are likely to be a biased subset with regard to survival.

Patient records were significantly more likely to have missing stage if the patient was aged over 75, women, more deprived, high grade tumour, not surgically treated or were diagnosed with rectal cancer (Table 3.12). Completeness of stage slightly improved with time, decreasing from 42% with missing stage in 1997 to 40% in 2004. Incomplete stage was very strongly associated with unknown grade, non-specific histology and

missing or no treatment, all of which are normally obtained (at least in part) from pathology reports. After adjustment, missing stage was significantly associated with patients over 85 at diagnosis, rectal and rectosigmoidal cancer, grade III & IV and no treatment. Missing stage was most strongly associated with treatment in both the unadjusted and adjusted analysis. This is because staging information for non-surgical patients is unlikely to be recorded or provided to cancer registrations, due to lack of pathology.

Table 3.12: Distribution of missing stage

Variables	Patients with mising or unknown stage		Unadjusted			Adjusted*		
	No.	%	OR	95% CI lower	95% CI upper	OR	95% CI lower	95% CI upper
Gender								
Men	6,612	53.9	1.0	-	-	1.0	-	-
Women	5,666	46.2	1.1	1.1	1.2	1.0	0.9	1.0
Age group								
15 to 44	304	2.5	1.0	-	-	1.0	-	-
45 to 54	738	6.0	0.8	0.7	1.0	0.7	0.6	0.9
55 to 64	1,889	15.4	0.8	0.7	0.9	0.6	0.5	0.8
65 to 74	3,457	28.2	0.9	0.8	1.0	0.7	0.6	0.8
75 to 84	3,964	32.3	1.2	1.0	1.4	0.7	0.6	0.8
85+	1,926	15.7	2.4	2.0	2.8	1.0	0.8	1.1
Deprivation								
1-affluent	1,901	15.5	1.0	-	-	1.0	-	-
2	2,081	17.0	1.1	1.0	1.2			
3	2,164	17.6	1.1	1.0	1.2			
4	2,435	19.8	1.1	1.0	1.2			
5-deprived	3,697	30.1	1.2	1.1	1.3			
Subsite (ICD-10)								
Colon (C18)	7,163	58.3	1.0	-	-	1.0	-	-
Rectosigmoid (C19)	864	7.0	0.9	0.8	1.0	1.2	1.1	1.3
Rectum (C20)	4,251	34.6	1.4	1.3	1.5	2.0	1.9	2.1
Grade								
Low	928	7.6	1.0	-	-	1.0	-	-
Moderate	4,129	33.6	0.9	0.8	0.9			
High	1,016	8.3	1.3	1.2	1.5			
Unknown	6,205	50.5	9.9	9.0	10.9			
Year of diagnosis								
1997	1,622	13.2	1.0	-	-	1.0	-	-
1998	1,546	12.6	0.9	0.8	1.0	0.8	0.8	0.9
1999	1,874	15.3	1.2	1.1	1.3	1.3	1.2	1.4
2000	1,403	11.4	0.7	0.7	0.8	0.7	0.6	0.7
2001	1,416	11.5	0.8	0.7	0.8	0.7	0.6	0.8
2002	1,440	11.7	0.9	0.8	1.0	0.7	0.7	0.8
2003	1,464	11.9	0.8	0.8	0.9	0.7	0.6	0.8
2004	1,513	12.3	0.9	0.8	1.0	0.8	0.7	0.9
Histology								
Neoplasms NOS	3,437	28.0	1.0	-	-	1.0	-	-
Adenocarcinomas	8,117	66.1	0.0	0.0	0.0	0.1	0.1	0.1
Muscinous and serous	620	5.1	0.0	0.0	0.0	0.1	0.1	0.1
Other	104	0.9	0.3	0.2	0.5	0.6	0.4	0.9
Treatment								
surgery only	5624	46.1	1.0	-	-	1.0	-	-
surgery & chemo	935	7.7	0.6	0.6	0.7	0.7	0.6	0.7
surg & xrt	554	4.5	0.9	0.8	1.0	0.6	0.6	0.7
surg, chemo & xrt	348	2.9	0.7	0.6	0.8	0.5	0.5	0.6
chemo only	387	3.2	3.8	3.2	4.5	3.5	2.9	4.2
chemo & radio	107	0.9	2.4	1.8	3.2	1.7	1.2	2.3
xrt only	192	1.6	4.2	3.3	5.4	2.8	2.1	3.6
no treat	4,056	33.2	18.2	16.5	20.1	9.7	8.7	10.8

* Adjusted for all variables in table

Histology

Histological type was grouped into adenocarcinoma, neoplasms NOS, mucinous and serous and other (Table 3.13) based on ICD-O-2 morphology codes system (Table 3.13). Mucinous and serous is a sub-type of adenocarcinoma and was the only sub-type

with sufficient numbers to analyse. The majority of colorectal cancers were adenocarcinomas (80.1%). Tumours with non-specific histology made up 11.6% of cases, with pathology unavailable for most of these patients. Mucinous or serous cancers accounted for 7.8% of cancers. The other category includes sarcomas (n=22), squamous cell (n=70) and specific epithelial (n=34) histological types.

Table 3.13: Histological groupings of ICD-O-2 morphology

Description	Morphology ICD-O-2	No.	%
Adenocarcinoma	81403, 81406, 81409, 81443, 81453, 82103, 83113, 82303, 82403, 82413, 82433, 82443, 82453, 82463, 82503, 82613, 82623, 82633, 85103, 85503, 82013, 82203, 82213, 83103	23,693	80.1
Neoplasm NOS	80003, 80013, 80103, 80106, 80109, 80043	3,428	11.6
Mucinous or serous	84403, 84703, 84803, 84806, 84806, 84809, 84813, 84903, 84906, 84303	2,314	7.8
Other	80203, 80213, 80216, 80223, 80413, 80323, 80503, 80703, 80713, 80726, 80723, 81233, 81243, 85603, 87203, 88003, 88903, 88503, 89003, 89803, 90803, 97203	128	0.4
Total		**29,563**	**100.0**

Deprivation

Socioeconomic group was assigned to each patient based on their Super Output Area (SOA) of residence at diagnosis. Patients were grouped in categories of deprivation using the Index of Multiple Deprivation (IMD) 2001[13] for patients diagnosed 1997-2004 at SOA. Most patients were in the two most deprived socioeconomic groups (most deprived: 29%, group 4: 19.5%) with the remaining three deprivation groups having similar proportions (17.7% to 16.4%).

Table 3.14: Distribution of cases by deprivation

Deprivation category	No.	%
Affluent - 1	4,855	16.4
2	5,080	17.2
3	5,214	17.7
4	5,774	19.5
Deprived - 5	8,640	29.2
Total	**29,563**	**100.0**

Deprivation categories were based on ecological measures of socioeconomic status obtain from the 2001 censuses and other government databases available for England, from the Office for National Statistics (ONS).[22] Socioeconomic information on income,

employment, health, disability, education, skills and training, barriers to housing, barriers to services, living environment and crime was available for geographic unit from the census and other government data bases. This was combined into a score for each small area of geography (SOA). However, only the income domain of the IMD was used as it is strongly associated with deprivation and excludes health-related variables, such as access to health services.[23] The inclusion of health related measures in the socioeconomic measure could result in overlap between the exposure measure (socioeconomic status) and variables under study (treatment).

Treatment

Eight treatment regimes were developed from the linked HES and cancer registry data: surgery only; surgery and chemotherapy; surgery and radiotherapy; surgery and chemoradiotherapy; chemotherapy only; chemoradiotherapy; radiotherapy only and no treatment (Table 3.15). Surgery and chemotherapy data were combined from HES and registry data while radiotherapy data were available only from cancer registry data (as described previously). Patients with no recorded treatment who could not be linked to any hospital admissions were assumed to have missing treatment data and multiple imputation methods were used to estimate the presence or absence of surgery, chemotherapy and radiotherapy (separately). Clinical information on surgical intent (i.e. curative, palliative) and chemotherapy (i.e. regime, adjuvant, neoadjuvant) was not available in population based datasets.

Table 3.15: Distribution of treatment regime

Description	No.	%
Surgery only	17,640	59.7
Surgery and chemotherapy	3,376	11.4
Surgery and radiotherapy	2,023	6.8
Surgery, chemotherapy and radiotherapy	1,181	4.0
Chemotherapy only	514	1.7
Chemotherapy and radiotherapy	182	0.6
Radiotherapy only	298	1.0
No treatment	4,349	14.7
Total	**29,563**	**100.0**

Absence of treatment data was significantly more common among patients who were older, with late stage disease, most deprived, had high grade tumours, and colon cancer (Table 3.16). Completeness of treatment data significantly decreased with time. Women were more likely to have missing data but this probably due to the later age at

diagnosis and this was only borderline significant after adjustment for age and other factors. Some of the associations with lack of treatment can be explained, at least in part, by clinical factors or methods of data collection. Poor prognosis is associated with late stage, high grade and older age. Patients with poor prognosis are less likely to receive surgery, chemotherapy or radiotherapy and hence their cancers are less likely to be pathologically confirmed. Without pathology grade and specific histological type can not be determined. In other studies, deprived patients have been found to have more incomplete data, although it is not clear why this occurs.[20,21]

Table 3.16: Distribution (No. and %) of patients with missing treatment by clinical factors, colorectal cancer patients diagnosed 1997-2004, North West of England

Variables	Patients with mising		Unadjusted			Adjusted*		
	No.	%	OR	95% CI		OR	95% CI	
				lower	upper		lower	upper
Gender								
Men	2,160	47.7	1.0	-	-	1.0	-	-
Women	2,369	52.3	1.4	1.4	1.5	1.1	1.0	1.2
Age group								
15 to 44	45	0.9	1.0	-	-	1.0	-	-
45 to 54	117	2.58	0.9	0.7	1.3	1.1	0.7	1.6
55 to 64	447	9.87	1.4	1.0	1.9	1.6	1.1	2.2
65 to 74	992	21.9	1.9	1.4	2.6	1.9	1.4	2.7
75 to 84	1,732	38.24	3.8	2.8	5.1	3.3	2.3	4.6
85+	1,196	26.4	9.8	7.2	13.4	5.8	4.1	8.2
Deprivation								
1-affluent	572.0	12.6	1.0	-	-	1.0	-	-
2	723.0	16.0	1.2	1.1	1.4	1.1	0.9	1.3
3	823.0	18.2	1.4	1.2	1.6	1.1	1.0	1.3
4	928.0	20.5	1.4	1.3	1.6	1.1	1.0	1.3
5-deprived	1483.0	32.7	1.6	1.4	1.7	1.3	1.1	1.5
Subsite (ICD-10)								
Colon (C18)	3,063	67.63	1.0	-	-	1.0	-	-
Rectosigmoid (C19)	232	5.12	0.5	0.5	0.6	0.7	0.6	0.8
Rectum (C20)	1,234	27.25	0.8	0.7	0.9	0.9	0.8	0.9
Grade								
Low	194	4.52	1.0	-	-	1.0	-	-
Moderate	887	20.68	0.9	0.8	1.1	1.0	0.8	1.1
High	291	6.78	1.7	1.4	2.1	1.4	1.1	1.7
Unknown	2,918	68.02	10.8	9.3	12.6	1.8	1.5	2.2
Year of diagnosis								
1997	504	11.13	1.0	-	-	1.0	-	-
1998	521	11.5	1.0	0.9	1.2	1.0	0.9	1.2
1999	542	11.97	1.0	0.9	1.2	0.9	0.8	1.1
2000	559	12.34	1.1	0.9	1.2	1.3	1.1	1.5
2001	583	12.87	1.1	1.0	1.3	1.5	1.2	1.7
2002	609	13.45	1.3	1.2	1.5	1.6	1.4	1.9
2003	630	13.91	1.3	1.1	1.5	1.4	1.2	1.7
2004	581	12.83	1.2	1.0	1.3	1.4	1.2	1.7
Histology								
Neoplasms NOS	2,439	53.9	1.0	-	-	1.0	-	-
Adenocarcinoma	1,939	42.8	0.0	0.0	0.0	0.2	0.2	0.2
Mucinous and serous	126	2.8	0.0	0.0	0.0	0.1	0.1	0.3
Other	25	0.6	0.1	0.1	0.2	0.2	1.6	2.0
Stage								
1	42	0.93	1.0	-	-	1.0	-	-
2	145	3.2	1.1	0.7	1.5	1.0	0.7	1.4
3	111	2.45	0.8	0.5	1.1	0.7	0.5	1.0
4	175	3.86	19.4	13.6	27.5	10.9	7.5	15.9
missing	4,056	89.56	26.5	19.5	36.0	11.7	8.5	16.1

*adjusted for all variables in table

Surgery type

Surgical excisions were defined through comparison with other studies,[9,24] and through specialist clinical advice (Table 3.17). Other surgery types included a broad range of procedures related to lower gastrointestinal cancer excision or general cancer excision (e.g. OPCS-4 T85 Block dissection of lymph nodes, T86 Sampling of lymph nodes). For patients who had more than one surgery the most radical surgery was taken to

define overall patient treatment. For example, patients having another type of surgery followed by colorectal excision (either in the same operation or on another day) would be grouped into the excision group for analysis.

The most common procedures for colon cancer patients were excision of the right hemicolon (25.1%) and excision of the sigmoid colon (11.3%). Anterior resection was most common among rectal cancer patients (23.9%) with a similar proportion having abdominoperineal excision (9.7%) or Hartman's procedure (9.9%).

Table 3.17: Type of Surgery

	Description	OPCS-4	No.	%
	Total excision of colon and rectum	H04	137	0.7
	Total excision of colon	H05	180	0.9
	Extended excision of right hemicolon	H06	1,029	5.3
	Excision of right hemicolon	H07	4,874	25.1
colon	Excision of transverse colon	H08	244	1.3
colon	Excision of left hemicolon	H09	1,370	7.1
colon	Excision of sigmoid colon	H10	2,201	11.3
colon	Excision of colon	H11	791	4.1
colon	Extirpation of lesion of colon	H12	174	0.9
rectal	Abdominalperineal excision of rectum	H331	1,887	9.7
rectal	Anterior resection of rectum	H332-4, H336	4,639	23.9
rectal	Hartman's procedure	H335	1,918	9.9
	Other surgery		4,776	16.2
	No surgery/missing	-	5,343	18.1
	Total		**29,563**	**100.0**

Surgeon volume

Yearly colorectal surgical work load was determined for each surgeon and assigned for that specific year to allow for new surgeons gaining experience with increasing surgical volume. For example, a surgeon may increase his/her surgery volume over time, conducting 15 surgeries in 1997, 25 in 1998 and 55 in 1999. They would have been assigned to the low-, mid- and high-volume surgeon categories for the patients they treated in 1997, 1998 and 1999, respectively. National guidance[25] recommends that colorectal cancer specialists should operate on a minimum threshold of 20 colorectal cases per year. Thus surgical volume of less than 20 patients per year and groupings of 20 were used to define surgeon volume (Table 3.18). Surgeons with the highest volume were also confirmed with local cancer registration officers.

There was a small group (3 to 5 depending on the year) of colorectal surgeons based at colorectal specialist centres and teaching hospitals that each conducted over 60

surgeries per year however these high volume surgeons only treated 2.3% of all North West colorectal patients. Most patients were treated by moderate (25.6%) or low volume (28.0%) surgeons. A substantial proportion of patients (12.7%) were known to have had surgery was but the surgeon was not recorded.

Table 3.18: Annual number of colorectal surgeries conducted for each surgeon

Surgeon volume		No.	%
very high	(over 60)	676	2.3
high	(40 to 59)	3,692	12.5
moderate	(20 to 39)	7,569	25.6
low	(less than 20)	8,530	28.9
surgery but consultant unknown		3,753	12.7
missing		2,640	8.9
no surgery		2,703	9.1
		29,563	**100.0**

Hospital volume

Hospital volume was assigned based on the volume of colorectal cancer surgeries conducted per year to take account of service changes and centralisation of some colorectal services. For example, a hospital may increase its surgery volume (probably due to centralisation) with time, conducting 35 in 1997, 65 in 1998 and 125 in 1999. They would have been assigned to the low-, mid- and high-volume hospital categories for the patients receiving surgery at that hospital in 1997, 1998 and 1999, respectively. Conversely, another hospital would decrease surgery volume over time, probably if centralisation occurred at another hospital.

There are no recommendations for annual colorectal surgery volume per hospital. An average district general hospital conducts colorectal cancer surgery on 100 patients per year so this was taken as a moderate volume.[25] Hospitals were grouped based on the annual volume of colorectal surgery during the study as low (less than 50), moderate (50 to 99), high (100 to 149), very high (more than 150) or private (Table 3.19). Information on private treatment was available for surgical patients and those who were treated at both private and NHS hospitals. Private hospitals commission the NHS to provide pathology reports and this is then available to cancer registries. For patients who are treated in the private sector and the NHS details, of treatment in private hospitals can be obtained from case-notes.

Table 3.19: Annual number of colorectal cancer surgeries per hospital

Hospital volume		No.	%
very high	(over 150)	1,402	4.7
high	(100 to 149)	4,594	15.5
moderate	(50 to 99)	8,282	28.0
low	(less than 50)	6,084	20.6
Private		576	2.0
Surgery but hospital not known		3,282	11.1
missing surgery		2,640	8.9
no surgery		2,703	9.1
Total		**29,563**	**100.0**

Comorbidity

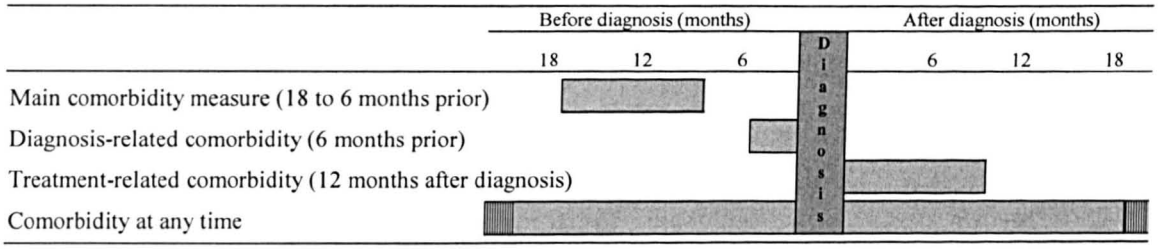
Comorbidity indices were derived from diagnostic codes associated with any hospital admission during 1997-2004, regardless of whether the admission was colorectal-related. The comorbidity scores of Charlson, Ghali and Elixhauser were assigned to each patient, based on their ICD-10 admission codes.[26-28] (Appendices 3 and 4) Information on previous malignancies, required for calculating the Charlson index, was obtained from NWCIS cancer registry data by searching the database back to 1981. Obtaining previous diagnosis from HES and cancer registry datasets will be compared in Chapter 5. Surgical eligibility and outcome can be influenced by hypertension (I10-I14, I20), ischaemic heart disease (I25), pulmonary embolism (I26) and obesity (E66), and therefore a 'moderated' Charlson score with these additions was also created for comparative evaluation as an alternative prognostic index.

Cancer registries have strict criteria for registering a definitive cancer diagnosis, while HES records may include a presumptive diagnosis while patients are undergoing complex diagnostic tests required to determine a cancer diagnosis. The prevalence of a previous non-colorectal tumour, or metastasis from any tumour was obtained from HES and cancer registry data. Based on HES data 33.4% of patients had a previous non-colorectal tumour and 11.8% with metastatic tumour based compared to 6% and 0.1% (n=15) based on cancer registry data, respectively. Cancer registry data was taken as a more robust measure of previous cancer diagnosis and used for the cancer comorbidity in the Charlson index.

The occurrence of comorbid conditions was calculated in three time windows in relation to the date of the cancer diagnosis: 18 to 6 months before diagnosis, the 6 months before diagnosis, in the first year after diagnosis and at any time (Figure 3.3). The impact of

comorbidity diagnosed at any time was evaluated, because this time-window is commonly used in other studies.

Figure 3.3: Time periods of comorbidity in relation to diagnosis



An individual comorbid condition contributed to the comorbidity score only if it occurred in the time period under evaluation. Multiple admissions for the same comorbidity within the same time window were counted only once.

$$index_j = \sum_{i}^{0} c_i * w_{c_i} * t_j$$

c_i = individual comorbidity

w_{c_i} = weight (only for Charlson)

$t = 0$ if comorbidity was not recorded in the relevant time period, or 1 if comorbidity was in the rele

j = time period of comorbidity (any time, 18 to 6 months before diagnosis, 6 months before diagnos 12 months after diagnosis)

Scores are all integer, with a possible range of 0 for no comorbidity to 28 for all possible comorbid conditions. They were grouped into four categories: 0 for no comorbidity and 1, 2 and 3 or more. Patients with no hospital admission (either colorectal or other cause) and no previous cancer were assumed to have missing data for the purposes of multiple imputation.

Life table data

The mortality and population data necessary to develop deprivation-, region- and period-specific life tables are available from the Office of National Statistics for England and Wales for 1991 and 2001 census data. Population and mortality data were available by five-year age group. Life tables are necessary for relative survival analysis in order to take into account of the background mortality.

Ethical and legal approvals

Ethical and legal approvals for this study were complex because of the overlap of this research and working within the NHS, and the need for identifiable data (Table 3.20).

Sponsorship by the host employer Christie NHS Foundation Trust, formerly the Royal Liverpool and Broadgreen University Hospitals Trust until May 2007 was required, because the study was undertaken by an employee and was required under the Research Governance Framework (DH 2001). Sponsorship in this context means, that the Trust is satisfied with the financial arrangements, that the study complies with Good Clinical Practice Guidelines and the Trust will take legal responsibility. The study received ethical approval from the Local Research Ethics Committee (Liverpool) and the London School of Hygiene and Tropical Medicine Ethical Committee. Approval from the Patient Information Advisory Group (PIAG) was obtained with the standard annual review (completed August 2007 and August 2008). Security and Confidentiality Advisory Group (SCAG) approval was required in order obtain identifiable Hospital Episode Statistics data (NHS number, date of birth and postcode).

Table 3.20: List of required approvals and ethical applications

Organisation	Approval date
Christie NHS Trust sponsoship (former sponsorship from Royal Liverpool and Broadgreen University Hospitals NHS Trust)	January 2006
Liverpool Research Ethics Committee (LREC)	March 2006
Patient Information Advisory Group (PIAG) (subject to annual review)	August 2006, renewed (August 2007, 2008)
Security and Confidentiality Advisory Group (SCAG) for access	September 2006
London School of Hygiene and Tropical Medicine ethical approval	September 2006

Summary

Data for this thesis will be a combination of cancer registry and hospital episode data to provide a complete record of treatment and comorbidity. Cancer registry data are generally of high quality, and complete for patient demographics and tumour details, but less complete for treatment data. These data were augmented with HES data to improve completeness. Despite the use of both HES and cancer registry data, incomplete data remained, most notably for stage at diagnosis, and this was managed through multiple imputation.

Appendix 3.1: Registry variables and definition

Tumour details:

Variable	Coding	Categorical groupings
Site	ICD-O-2	
Morphology	ICD-O-2	
Grade	1,2,3,4,9	1 - well differentiated 2 - moderately differentiated 3 - poorly differentiated 4 - undifferentiated 9 - not known
Date of diagnosis	dd/mm/yyyy	
Stage	1,2,3,4,6	1 - stage I 2 - stage II 3 - stage III 4 - stage IV 6 - not known
Dukes (or amended Dukes/Astler-Collier)	A, B, C, D (or A, B1, B2, C1, C2, D)	Dukes' A - tumour penetrates into the submucosa of the bowel Dukes' B – tumour invades muscularis propria Dukes' C - tumour invasion with regional lymph nodes involved Dukes' D - tumour, has spread beyond the confines of the lymph nodes (to organs such as the liver, lung or bone) Amended Dukes/Astler-Collier is based on Dukes' but the A, B1 B2, C1, C2 and D have slightly different definitions. They have not been listed here for brevity.
T	X,0,1,2,3,4	X - primary tumour can not be assessed 0 - no evidence of primary tumour 1 - tumour invades the submucosa 2 - tumour invades muscularis propria 3 - tumour invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues 4 - tumour directly invades the other organs or structures, and/or perforates visceral peritoneum
N	X,0,1	X - regional lymph nodes cannot be assessed 0 - no regional lymph node metastasis 1 - metastases in 1 to 3 regional lymph nodes 2 - metastases 4 or more regional lymph nodes
M	X,0,1	X - distant metastasis cannot be assessed 0 - no distant metastasis 1 - distant metastasis

Tumour details continued.		
Variable	**Coding**	**Categorical groupings**
Basis of diagnosis	1,2,3,4,5,6,7,8,9	1 or 2 - histology 3 - cytology 4 - haematology 5 - special test 6 - imaging 7 - observation 8 - clinical 9 - not known
Source of registration	1,2,3,4,5,6,9	1 - pathology 2 - cytology 3 - haematology 4 - hospital records 5 - other registries 6 - death certificate 9 - not known
Death certificate only (Patients for whom cancer is notified from death certificate, and first hospital and GP review finds no cancer diagnosis or cancer treatment.)	Yes/No	

Treatment details:

Variable	**Coding**	**Categorical groupings**
First reported date of diagnosis or treatment	dd/mm/yyyy	
Date of first hospital attendance (and subsequent attendances)	dd/mm/yyyy	
Hospital of first attendance (and hospital for any subsequent attendances)	Hospital reference code	Corresponds to look-up table with hospital name and address.
Date of treatment (for each of radiotherapy, chemotherapy or surgery) within 6 months of diagnosis	dd/mm/yyyy	
Treatment information available for each separately surgery, chemotherapy, radiotherapy	Code for type of surgery, chemotherapy and/or radiotherapy	Corresponds to look-up table with type of treatment details.
Consultant treating	GMC code	
Hospital of treatment	Hospital reference code	Corresponds to look-up table with hospital

Patient details:

Variable	**Coding**	**Categorical groupings**
Patient postcode	Text	
Sex	1,2	1 – male, 2 -female
Date of birth	dd/mm/yyyy	
Date of death	dd/mm/yyyy	

Appendix 3.2: OPCS-4 surgical codes for colorectal cancer surgery (either alone or in combination)

OPCS-4 (3-digit)	General description	No. of procedures (first procedure)	%
G07	Repair of oesophagus	3	<0.1
G27	Total excision of stomach	3	<0.1
G28	Partial excision of stomach	50	0.2
G29	Open extirpation of lesion of stomach	15	0.1
G30	Plastic operations on stomach	1	<0.1
G33	Other connection of stomach to jejunum	33	0.1
G47	Intubation of stomach	1	<0.1
G49	Excision of duodenum	1	<0.1
G58	Excision of jejunum	1	<0.1
G61	Bypass of jejunum	2	<0.1
G69	Excision of ileum	99	0.4
G70	Open extirpation of lesion of ileum	4	<0.1
G71	Bypass of ileum	18	0.1
G72	Other connection of ileum	5	<0.1
G74	Creation of artificial opening into ileum	47	0.2
G75	Attention to artificial opening into ileum	1	<0.1
H01	Emergency excision of appendix	42	0.2
H02	Other excision of appendix	136	0.5
H03	Other operations on appendix	2	<0.1
H04	Total excision of colon and rectum	115	0.5
H05	Total excision of colon	156	0.6
H06	Extended excision of righ hemicolon	918	3.7
H07	Other excision of right hemicolon	4,546	18.2
H08	Excision of transverse colon	207	0.8
H09	Excision of left hemicolon	1,165	4.7
H10	excision of sigmoid colon	1,770	7.1
H11	other excision of colon	708	2.8
H12	Extirpation of lesion of colon	148	0.6
H13	Bypass of colon	143	0.6
H14	Exteriorisation of caecum	38	0.2
H15	other exteriorisation of colon	2,165	8.6
H16	Incision of colon	8	<0.1
H17	Intraabdominal manipulation of colon	4	<0.1
H18	Open endoscopic operations on colon	3	<0.1
H19	Other open operations on colon	17	0.1
H20	Endoscopic extirpation of lesion of colon	613	2.4
H21	Other therapeutic endoscopic operations on colon	13	0.1
H22	Diagnostic endoscopic examination of colon	605	2.4
H23	Endoscopic/extirpation/lesion/Lower bowel using fiberoptic sigmoidoscopy	491	2.0
H24	Other therapeutic endoscopic operations on lower bowel using fiber optics	58	0.2
H26	Endoscopic/extirpation/lesion/ colon using rigid sigmoidoscopy	85	0.3
H27	Other therapeutic endoscopic operations of the sigmoid colon using rigid sigmoidoscopy	21	0.1
H30	Other operations on colon	30	0.1
H33	Excision of rectum	4,922	19.7

continued.

OPCS-4 (3-digit)	General description	No. of procedures (first procedure)	%
H34	Open extirpation of lesion of rectum	38	0.2
H40	Operations on rectum through anal sphincter	34	0.1
H41	Other operations on rectum through anus	568	2.3
H42	Perineal operations for prolapse of rectum	1	<0.1
H44	Manipulation of rectum	269	1.1
H46	Other operations on rectum	26	0.1
H48	Excision of lesion of anus	23	0.1
H54	Dilation of anal sphincter	6	<0.1
H55	Other operations on perianal region	5	<0.1
H56	Other operations on anus	18	0.1
H58	Drainage through perineal region	10	<0.1
H60	Other operations on pilonidal sinus	1	<0.1
H62	Other operations on bowel	25	0.1
J02	Partial excision of liver	11	<0.1
J03	Extirpation of lesion of liver	1	<0.1
J05	Incision of liver	7	<0.1
J18	Excision of gall bladder	5	<0.1
J57	Other partial excision of pancreas	1	<0.1
J69	Total excision of spleen	4	<0.1
M02	Total excision of kidney	1	<0.1
M34	Total excision of bladder	1	<0.1
M35	Partial excision of bladder	2	<0.1
M42	Endoscopic extirpation of lesion of bladder	5	<0.1
Q07	Abdominal excision of uterus	14	0.1
Q23	Unilateral excision of adnexa of uterus	2	<0.1
Q24	Other excision of adnexa of uterus	1	<0.1
T28	Other repair of anterior abdominal wall	1	<0.1
T29	Operation on umbilicus	1	<0.1
T30	Opening of abdomen	138	0.6
T31	Other operations on anterior abdominal wall	11	<0.1
T33	Open extirpation of lesion of peritoneum	1	<0.1
T34	Open drainage of peritoneum	10	<0.1
T36	Operations on omentum	8	<0.1
T38	Operations on mesentery of colon	2	<0.1
T41	Other open operation on peritoneum	26	0.1
T42	Therapeutic endoscopic opertion on peritoneum	1	<0.1
T43	Diagnostic endoscopic examination of peritoneum	15	0.1
T45	Image controlled operations on abdominal cavity	16	0.1
T46	Other drainage of peritoneal cavity	87	0.3
T85	Block dissection of lymph nodes	1	<0.1
T86	Sampling of lymph nodes	3	<0.1
T87	Excision or biopsy of lymph node	12	<0.1
X14	Clearance of pelvis	4	<0.1
Z28	Large intestine	2,098	8.4
Z29	Other part of bowel	2,110	8.4
	Total	**25,037**	

Appendix 3.3: Charlson, amended Charlson and Ghali comorbidity ICD-10 codes and weights.

Assigned weight	Comorbidity	ICD-10	Source	Charlson	Ghali
1	Myocardial infarction	I21.x, I22.x, I25.2	HES	✓	✓
1	Congestive heart failure	I09.9, I11.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0	HES	✓	✓
1	Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	HES	✓	✓
1	Cerebrovascular disease	G45.x, G46.x, F05.1, G30.x, G31.1	HES	✓	✓
1	Dementia	F00.x-F03.x, F05.1, G30.x, G31.1	HES	✓	
1	Chronic pulmonary disease	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3	HES	✓	
1	Rheumatic disease	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0	HES	✓	
1	Peptic ulcer disease	K25.x-K28.x	HES	✓	
1	Mild liver disease	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4	HES	✓	
1	Diabetes without chronic complication	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8.	HES	✓	
2	Diabetes with chronic complication	E10.2-E10.5, E10.7, E11.1-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7	HES	✓	✓
2	Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9	HES	✓	
2	Renal disease	I12.0, I121.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0,	HES	✓	✓
3	moderate of sever liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	HES	✓	
6	AIDS/HIV	B20.x-B22.x, B24.x	HES	✓	
3	Any malignancy**	C00.x-C43.x, C45.x-C77.x, C81.x-C97.x	Cancer Registry	✓	
6	Other metastatic solid	C77.x-C80.x	Cancer Registry	✓	
Additional disease categories:					
1	Hypertension	I10.x-I14.x, I20.x	HES	Addition	
1	Ischaemic heart disease	I25.0, I25.1, I25.3, I25.4, I25.6, I25.8, I25.9	HES	Addition	
1	Pulmonary embolism	I26.x	HES	Addition	
1	Obesity	E66.x	HES	Addition	

Appendix 3.4: Elixhauser comorbidity index ICD-10 codes.

Comorbidity	Elixhauser (ICD-10)
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I43.0, I42.5-I42.9, I43.x, I50.x, P29.0
Cardiac arrhythmias	I44.1-I44.3, I45.6, I45.9, I47.x-I49.x, R00.0, R00.1, R00.8, T82.2, Z45.0, Z95.0
Valvular disease	A52.0, I05.x-I08.x, I09.1, I09.8, I34.x-I39.x, Q23.0-Q23.3, Z95.2-Z95.4
Pulmonary circulatory disorders	I26.x, I27.x, I28.0, I28.8, I28.9
Peripheral vascular disorders	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9,
Hypertension, uncomplicated	I10.x
Hypertension, complicated	I11.x-I13.x, I15.x
Paralysis	G04.1, G11.4, G80.1, G80.2, G80.x, G82.x, G83.0-G83.4, G83.9
Other neurological disorders	G10.x-G13.x, G20.x-G22.x, G25.4, G25.5, G31.2, G31.8, G31.9, G32.x, G35.x-G37.x, G40.x, G41.x, G93.1, G93.4, R47.0, R56.x
Chronic pulmonary disease	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Diabetes, uncomplicated	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes, complicated	E10.2-E10.8, E11.2-E11.8, E12.2-E12.8, E13.2-E13.8, E14.2-E14.8
Hypothyrodism	E00.x-E03.x, E89.0
Renal failure	I12.0, I13.1, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z99.2
Liver disease	B18.x, I85.x, I86.4, I98.2, K70.x, K71.1, K71.3-K71.5, K71.7, K72.x-K74.x, K76.0, K76.2-K76.9, Z94.4
Peptic ulcer disease, excluding bleeding	K25.7, K25.9, K26.7, K26.9, K27.7, K27.9, K28.7, K28.9
HIV/AIDS	B20.x-B22.x, B24.x
Lymphoma	C81.x-C85.x, C88.x, C96.x, C90.0, C90.2
Solid tumour	C00.x-C26.x, C30.x, C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C97.x
Metastatic tumour	C77.x-C80.x
Coagulopathy	D65-D68.x, D69.1, D69.3-D69.6
Obesity	E66.x
Weight loss	E40.x-E46.x, R63.4, R64
Fluid and electorlyte disorders	E22.2, E86.x, E87.x
Blood loss anemia	D50.0
Deficiency anemia	D50.8, D50.9, D51.x-D53.x
Alcohol abuse	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4,
Drug abuse	F11.x-F16.x, F18.x, F19.x, Z71.5, Z72.2
Psychoses	F20.x, F22.x-F25.x, F28.x, F29.x, F30.2, F31.2, F31.5
Depression	F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, F43.2

Reference List

(1) Connecting for Health. NHS Data model and dictionary service. 2005. Available from URL: http://www.nhsia.nhs.uk/datastandards/pages/dd/data_dictionary/messages/national_cancer_data_set/

(2) International Classification of Diseases for Oncology. Second ed. Geneva: World Health Organisation; 2008.

(3) Pheby DFH, Levine DF, Pitcher RW, Shepard NA. Lymph node harvests directly influence the staging of colorectal cancer: evidence from a regional audit. *Journal of Clinical Pathology.* 2004; 57:43-47.

(4) IARCtools [Lyon: IARC; 1999.

(5) The information centre. Data Quality Indicator (DQI) Reports. 2008. (cited 17 Mar. 2008) Available from URL: www.hesonline.nhs.uk

(6) Westaby S, Archer N, Manning N, Aswani S, Grebenik C, Ormerod O, Pillai R, Wilson N. Comparison of hospital episode statistics and central cardiac audit database in public reporting of congenital heart surgery mortality. *British Medical Journal.* 2007; 335:759-784.

(7) The information centre. HESonline. 2008. (cited 2 May 2008) Available from URL: www.hesonline.nhs.uk

(8) Stat/Transfer [Seattle: Circle Systems; 2005.

(9) Morris E, Quirke P, Thomas JD, Fairley L, Cottier B, Forman D. Unacceptable variation in abdominoperineal excision rates for rectal cancer: time to intervene? *Gut.* 2008; 12:1690-1697.

(10) The association of coloproctology of Great Britian and Ireland. The National Bowel Cancer Audit Programme. 2009. (cited 10 May 2008)

(11) UKACR coding and classification group. *Library of recommendations on coding and classificantion policy and practice.* London: UKACR, 2008.

(12) Schottenfeld D, Winawer SJ. Cancers of the large intestine. In: Schottenfeld D, Fraumeni JF Jr, editors. *Cancer Epidemiology and Prevention.* 2nd ed. Oxford: Oxford University Press, 1996, 813-840.

(13) Dukes CE. The classification of cancer of the rectum. *Journal of Pathology and Bacteriology.* 1932; 35:323.

(14) Astler VB, Coller FA. The prognostic significance of direct extension of carcinoma of the colon and rectum. *Annals of Surgery.* 1954; 139:846.

(15) Thomson C.on behalf of the Quality Assurance Group of the UK Association of Cancer Registries. *Annual Performance Indicators Report, 2006.* Birmingham: UKACR, 2006.

(16) Royston P. Multiple imputation of missing values. *Stata Journal.* 2004; 4:227-241.

(17) STATA statistical software [College Station, TX: Stata Corporation; 2004.

(18) Green J, Watson J, Roche M, Beral V, Patnick J. Stage, grade, and morphology of tumours of the colon and rectum recorded in the Oxford Cancer Registry, 1995-2003. *British Journal of Cancer.* 2007; 96:140-142.

(19) Adams J, Audisio RA, White M, Forman D. Age-related variations in progression of cancer at diagnosis and completeness of cancer registry data. *Surgical Oncology.* 2005; 13:175-179.

(20) Adams J, White M, Forman D. Are there socioeconomic gradients in stage and grade of breast cancer at diagnosis? Cross sectional analysis of UK cancer registry data. *British Medical Journal.* 2004; 329:142-143.

(21) Adams J, White M, Forman D. Are there socioeconomic gradients in the quality of data held by registries? *Journal of Epidemiology and Community Health.* 2004; 58:1052-1053.

(22) ONS. Census 2001. 2006. (cited 1 Sept. 2006) Available from URL: www.statistics.gov.uk/census2001

(23) Woods LM, Rachet B, Coleman MP. Choice of geographic unit influences socioeconomic inequalities in breast cancer survival. *British Journal of Cancer.* 2005; 92:1279-1282.

(24) Tilney HS, Tekkis PP, Heriot AG, Lovegrove RE, Smith JJ, Thompson MR, Stamatakis JD, on behalf of the Association of Coloproctology of Great Britian and Ireland. *Report of the National Bowel Cancer Audit Project "Assessing Quality".* London: The Association of Coloproctology of Great Britian and Ireland, 2006.

(25) Department of Health. *Improving outcomes in colorectal cancer: the manual.* London: Department of Health, 1997.

(26) Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care.* 2005; 43:1130-1140.

(27) Elixhauser A, Steiner C, Harris DR, Coffey R. Comorbidity measures for use with administrative data. *Medical Care.* 1998; 36:8-27.

(28) Ghali WA, Hall RE, Rosen AK. Searching for an improved clinical comorbidity index for use with ICD-9-CM administrative data. *Journal of Clincal Epidemiology.* 1996; 49:273-278.

Chapter 4

Methodology

Overview

Relative survival is the gold standard for analysing population-based cancer registry data. Relative survival estimates cancer survival in the absence of other causes of death by taking into account the underlying mortality in the population which is particularly important when comparing socioeconomic groups with different underlying mortality, as in this thesis. By applying Poisson regression using generalized linear models (GLM) on estimated excess deaths multivariable analysis can be done that assesses the contribution of each prognostic factor and inter-relationships between prognostic factors. The resulting multivariable estimate is known as an excess hazard of death.

Missing data for treatment and stage remain even after the use of both cancer registry data and HES. There are a number of different approaches to handling missing data including 'ad hoc' approaches such as excluding cases with missing data or analysing them in a separate category. However these approaches can introduce bias if patients without complete data are different (e.g. later stage) than those with complete data. Multiple imputation provides an alternative approach by imputing, or filling-in, missing data thus allowing standard analytical techniques, such as relative survival and the excess hazard of death.

Survival analysis

Analysis of survival has become an increasingly important tool for assessing improvements in patient outcome. Population-based cancer registries collect data that enable accurate estimates of survival for the cancer patients of the resident population.[1] Survival is simply defined as the probability that a person with a given disease will be alive at a specified time (t_i) since diagnosis. Survival is estimated as the product of the conditional survival probabilities for all time intervals (t_i) in the follow-up period. Conditional probability is the probability of surviving the interval conditional on being alive at the start of the interval.[2] Survival should not be calculated simply as the proportion of patients alive (out of the number of patients at risk) because it does not correctly account for censored[10] patients. In the Kaplan-Meier[3] method, survival is constant over each interval.[1]

$$S(t) = \prod_{t_i \le t} \left(1 - \frac{d_i}{n_i} \right) \qquad (1)$$

$S(t)$ = Survivor function at t_i

t_i = Duration of study at t_i

d_i = Number of deaths occurring at t_i

n_i = Number of patients at risk just prior to t_i

$1 - \frac{d_i}{n_i}$ = Conditional probability of surviving to t_i

i = survival interval i

Survival can be conceptualised according to two main concepts: the observed survival and the net survival. For simplicity, we will often use the complement of survival, i.e. the mortality, to explain concepts.

Main concepts in population-based survival

Observed (or crude) survival

According to the theory of competing risks,[4,5] the overall probability of death observed within a given population may be defined as the sum of the probabilities for each cause of death. Therefore, the overall observed probability of death does not reflect only the lethality of the disease of interest. This may lead to biased conclusions particularly if

[10] When a patient is alive at the end of follow-up, or lost to follow-up during the study, the follow-up time is stopped either when they are lost to follow up or at the end of complete follow-up for the population, or earliest.

many deaths within cancer patients are not cancer related, e.g. in the elderly. This is a particular issue with cancer survival because cancer is mainly a disease of the elderly, a considerable proportion of deaths in cancer patients may be due to non-cancer causes. In such situations, the observed mortality, and by extension the observed survival may reflect the background mortality rather than the mortality related to the cancer of interest.

The probability of death from the cancer under study is the parameter of interest. This corresponds to the net probability of death, which is the probability of death from the cancer when all risks of death from other causes have been eliminated. The same definition stands with the complement of the mortality, or the survival probabilities.

$$\text{Observed mortality} = \sum \text{cause}_i \text{ mortality} = \sum (\text{cause}_{i-1} \text{ mortality}) + \text{cancer mortality}$$

$$\text{Cancer survival} = 1 - (\text{observed mortality} + \sum \text{cause}_{i-1} \text{ mortality})$$

i = survival interval

Net survival

The net probability of cancer death is the probability of dying from the cancer in the absence of other causes of death. Its complement, the net cancer survival, is obtained if the risk of death from causes other than the cancer is removed. The underlying assumption is that the cause of death of interest is independent of other competing causes of death. Cause-specific and relative survival both attempt to measure net survival.

Cause-specific survival

Cause-specific survival is based on only patients dying of the disease of interest (i.e. cancer or colorectal cancer). Those dying of other causes are censored at death.

In population-based data, such as cancer registries, cause of death is obtained from the patient's death certificate. Cause of death obtained from death certificates has been proven not to be reliable enough for cause-specific survival analysis.[6] With only the death certificate information it is difficult to determine if cancer is the main or underlying cause of death.[1] In practice the use of cause-specific survival is usually limited to clinical trials where detailed and unbiased cause of death is available. Cause-specific analysis will not be performed in this thesis for these reasons.

Relative survival

Relative survival has become the 'gold standard' method for estimating cancer survival in population-based databases, such as the UK cancer registries. Relative survival attempts to estimate survival of cancer patients in the absence of other causes ob death (non-cancer) by taking into account the underlying mortality in the population from which the cancer patients are drawn (E_i). It is the ratio of overall survival ('observed survival' as described earlier) in the cancer patient population (S_i) to the survival that would have been expected in the cohort of patients if they had been subject to the mortality rate of the population from which they come from ('background' or 'expected survival' (E_i)). Consequently, the excess mortality risk associated with the cancer population may be thought to be based on the cancer deaths and cancer-associated deaths, such as complications related to cancer treatment, that would not have occurred without the cancer.

The background mortality is obtained from life tables (see life tables section) which are defined at least by age, sex and calendar period. The background risk of death may vary with other factors such as region or socioeconomic status, and such variables may be included in specific life tables. Although the life tables include deaths due to cancer, this has little or no impact on the estimated background risks of death.[2,6,7]

$$R_i = S_i / E_i \tag{2}$$

R_i = Relative survival
S_i = Survival in the cancer population
E_i = Survival in the underlying population
i = survival interval

Modelling excess mortality

When there are several prognostic factors to compare and adjust for, univariable survival analysis is too simplistic and the need for more complex models arises. Regression models for excess mortality are the most practical method of assessing the impact of multiple factors on survival.[8] Various approaches have been used to model excess mortality with most using on the maximum likelihood model based on the underlying additive hazards model.[2]

$$\lambda(x) = \lambda * (x) + \exp(x\beta) \tag{3}$$

$\lambda(x)$ = observed hazard for patients diagnosed with cancer
$\lambda*(x)$ = expected hazard function (estimated from external data i.e. life tables)
$\exp(x\beta)$ = excess hazard
x = covariate vector
β = varying parameter

The regression model (with covariate x) is estimated as the sum of the expected hazard ($\lambda*(x)$) and the excess hazard associated with a cancer diagnosis ($\exp(x\beta)$). The expected hazard ($\lambda*(x)$) is obtained from life tables and has a specific subset of covariates which are available in the life tables (e.g. age, sex, calendar period and socioeconomic status) but does not depend on all covariates in the analysis (e.g. stage or histology).[2] The excess hazard ratio estimated by such models can be thought of as the probability of dying from the cancer in the presence of the factor divided by those in the absence of the factor,[9] or as a risk ratio for mortality.

The model is estimated in the framework of GLM using a Poisson assumption for the distribution of the number of observed deaths. The Poisson distribution is necessary because observed deaths and excess mortality is skewed towards earlier time periods since diagnosis (or 'right skewed'). We assume the number of deaths (d_j) for a subject band (j) can be described by a Poisson distribution ($d_j \sim Poisson(u_j)$) where $u_j = \lambda_j y_j$ (λ_j is the expected hazard function and y_j is person-time at risk) (Equation 3 & 4).[2] For grouped analysis of the hazard ratio of excess mortality data is aggregated by the variables under study (e.g. combination of age group, sex, follow-up interval) into subject bands.

$$u_j / y_j = d_j^* / y_j + \exp(x\beta) \tag{4}$$

or

$$\ln(u_j - d_j^*) = \ln(y_j) + \exp(x\beta) \tag{5}$$

d_j^* = expected number of deaths (due to causes other than cancer of interest)

y_j = person-time at risk for observation (taken from life tables)

j = subject j (or aggregation e.g. men aged 55 to 60)

This implies a generalized linear model with Poisson error structure (link $\ln(u_j - d_j^*)$ and offset $\ln(y_j)$). The assumption that $d_j \sim Poisson(u_j)$ is introduced in order to use the GLM approach but is not strictly necessary.

Excess hazards are assumed to be proportional along the analysis follow-up time.[2] Proportionality may not be true in many instances, for example patients who received surgery, compared to those not undergoing surgery, may have high excess hazards post-operatively and low later. If we falsely assume proportionality, we run the risk of misinterpreting or over-looking significant associations across time.[10] When non-proportionality occurs it is possible to model the variable with time-by-covariate interaction terms,[2] either through stepwise functions or more flexible functions such as splines.[11] Currently, splines are not available in statistical software with methods for analysing imputed data and we opt for modelling the variables with stepwise approaches.

There are a number of comparable approaches to estimating the excess hazard of death including full-likelihood approach,[12] Hakulinen-Tenkanen[13] and Poisson models. These approaches differ mainly in the way the data is presented (individual, aggregated) and assumptions (distributions) but produce similar estimates of the excess hazard of death.[2] Due to the similarity of estimates in practice the choice of model may guided by the availability of software and ease of use.[2] Taking all these factors into consideration the generalized linear model with a Poisson error function on aggregated data using exact survival estimates were the recommended method for regression analysis of excess death.[2] Some cancer registries outside of the UK record survival in complete years, rather than exact survival time.[6] In this study exact survival time (e.g. complete date of death and survival time in days) was available enabling analysis at intervals narrower than yearly. The number of excess deaths was estimated using individual data by a combination of variables to be studied for Poisson analysis of excess hazard of death. This approach was taken, rather than the comparable poisson regression of relative survival, in part because it was already available within multiple imputation software in STATA, however both approaches to estimating the excess hazard of death produce similar estimates.[2,14]

Survival analysis designs

Cohort design

Cohort survival requires all patients in the analysis to have a potential follow-up time which is equivalent to the specified time since diagnosis under study, e.g. five years. Patients who are lost to follow-up or die are censored, as previously described. In the example below (Figure 4.1), patients diagnosed in 1997 would be followed up until 2002, at which point five years of follow-up were available and five-year survival could be calculated. Cohort survival requires a long period of follow-up but because the major influences of survival occur in the first few years after diagnosis, mostly in the first year, complete analysis will be used to provide more timely estimates.

Complete design

Complete survival includes all patients diagnosed during a specified time period. Within the defined period some, but not all patients would be followed up for at least five years. For example complete survival can be used to estimate five-year survival for patients diagnosed during 1997 to 2004, despite patients diagnosed in 2004 only having three years of follow-up.

Period and hybrid designs

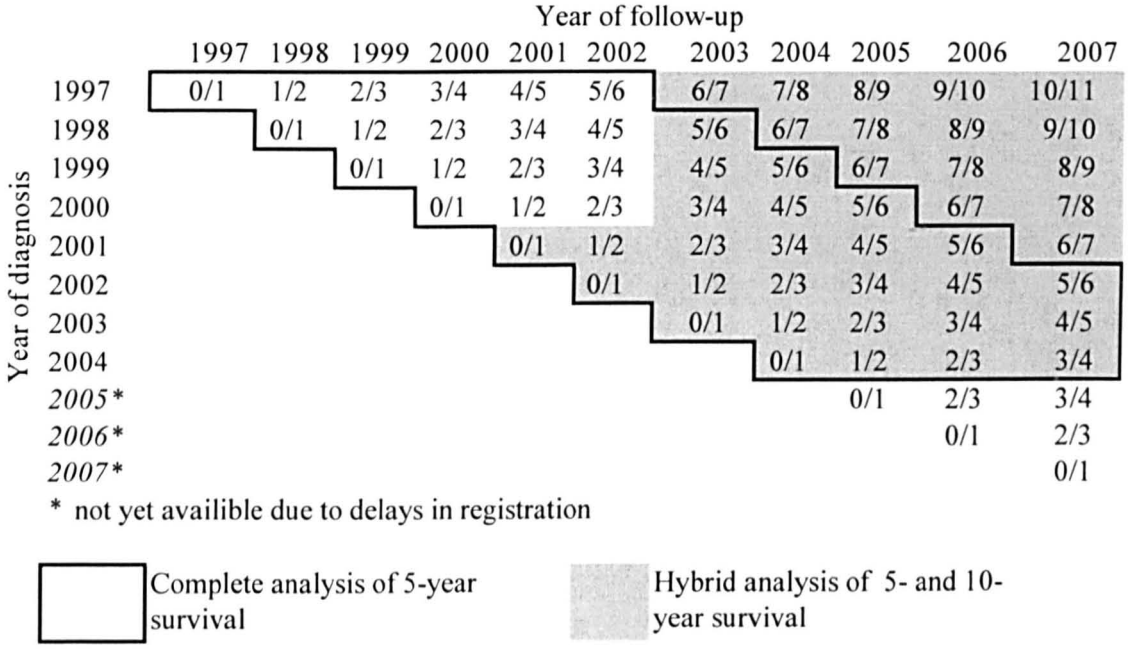
Period survival is a method for predicting survival by incorporating the conditional probabilities of the most recently diagnosed patients into survival analysis.[15-18] The period survival approach can be though of as analogous to estimates of the life expectancy at birth, where the mortality in the current population is used to estimate life expectancy. This method enables the estimation of five-year survival before five years of follow-up was available for all patients. The advantage of this method is that by including recently diagnosed patients it produces more up-to-date and timely survival estimates that incorporate the effect of new advances in treatment and their impact on survival.[19]

Period survival uses the patients' survival experience in the most recent period. For example to estimate five-year survival in 2005 we use 0- to 1-year survival experience for cases diagnosed in 2004, 1- to 2-year survival experience for cases diagnosed in 2003 for patients who survived at least 1 year, and so on up to 4- to 5-year survival for patients diagnosed in 2001 who survived at least 4 years. Period survival is then estimated by multiplying these probabilities.[19] Period relative survival has been tested

against standard relative survival methods and was found to reliably predict short-term and long-term survival estimates.[20,21]

When incidence data are less up-to-date than mortality data, as occurs in cancer registry data, survival is biased and the hybrid approach should be used.[22] The hybrid approach combines elements of cohort, complete and period analyses to provide unbiased short-term survival estimates and smaller variance than traditional period survival. For example the hybrid approach would analyse patients diagnosed 2003 and 2004, with patients diagnosed earlier (1997 to 2002) and still alive up-to 2007 included.

Figure 4.1: A diagram of the years of follow-up used for cohort and hybrid survival approaches



Life tables

Life tables provide estimates of the underlying population mortality necessary to calculate relative survival and excess mortality. The relative survival algorithm uses the probability of dying (q_x) to estimate the expected population mortality rate. For this thesis, life tables by age, sex, deprivation and for the North West of England were developed from 1991 and 2001 census data. Population and mortality data were available by five-year age group. In order to estimate mortality rates for all ages (0 to 100) and to even out random variations which may occur due to few deaths or small populations, particularly at the youngest and oldest ages, mortality rates were extrapolated and smoothed to single years of age using the Ewbank approach.[23]

Multiple imputation

It has often been considered that the simplest, approach to analyse a dataset with missing data was to exclude patients with missing data, and to conduct analyses on the remaining cases (complete-case analysis). Limiting the analysis to patients with complete data would thus substantially reduce the size of the analysed dataset, waste data and produce inefficient estimates of the excess hazards of death and may then introduce bias resulting in misleading conclusions.[24-27] Cases with 'missing' data for a given variable (e.g. stage) can also be included in the analysis by assigning a separate category for patients with missing data (e.g. stage not known), or by assigning the mean value for that variable. To avoid biasing results these 'ad hoc' methods require the implicit assumption that patients with missing data are not systematically different with regard to variables of interests (e.g. stage, survival) from those with complete data, a mechanism of missingness also known as missing completely at random (MCAR).[25]

Completeness of stage data and other variables in population-based registries varies by age,[28] geography,[29,30] and socioeconomic status,[31] making 'ad hoc' approaches inappropriate. Alternatively, 'missing' data can be imputed, with regression techniques, and the final imputed dataset analysed with standard methods, thereby minimising bias compared to 'ad hoc' approaches, and increasing power.[32] In the past the method of multiple imputation was limited by computational power and unavailability of software in the standard statistical packages, however multiple imputation is now established as a standard method of analysing datasets with missing data.[24,33-36] To my knowledge it has been rarely used for analysis of cancer data[26,37,38] and colorectal cancer patients.[39]

Assumptions

The method of handling missing data depends on the mechanism believed to underlie the missing values, which can follow three types:[32]

a) Missing Completely at Random (MCAR)

b) Missing At Random (MAR)

c) Missing Not At Random (MNAR)

MCAR occurs when the probability of an observation (r) being missing is random, and therefore does not depend on either the explanatory variables or outcome (z). In these situations, the missing cases can be excluded from the analysis and valid inferences can be made, although this will result in some loss of statistical power.[40]

$$P(r|z) = P(r) \tag{6}$$

MAR occurs when, given the observed data, the probability of missing information (e.g. stage) does not depend on the unobserved data (e.g. education).[41] This is the most commonly assumed mechanism and enables the imputation of missing observations using likelihood methods under the assumption that the mechanism of missingness can be explained by the observed data. The MAR assumptions can not be tested or definitively determined, without obtaining the missing data but is generally robust to errors in the underlying assumptions.

$$P(r|z) = P(r|z_0) \tag{7}$$

Observations that are not MCAR or MAR are considered Missing Not at Random (MNAR). When data are MNAR they can not be explained by the observed data in the data set and depend on unrecorded observations.[41] If the mechanism of missing data is MNAR, the probability of missing stage would depend on variables in our data set (e.g. age, sex, hospital) and variables which are not in our data set (e.g. education, genetic predisposition, health-seeking behaviour). It is difficult to determine the appropriate imputation model for MNAR data.[41]

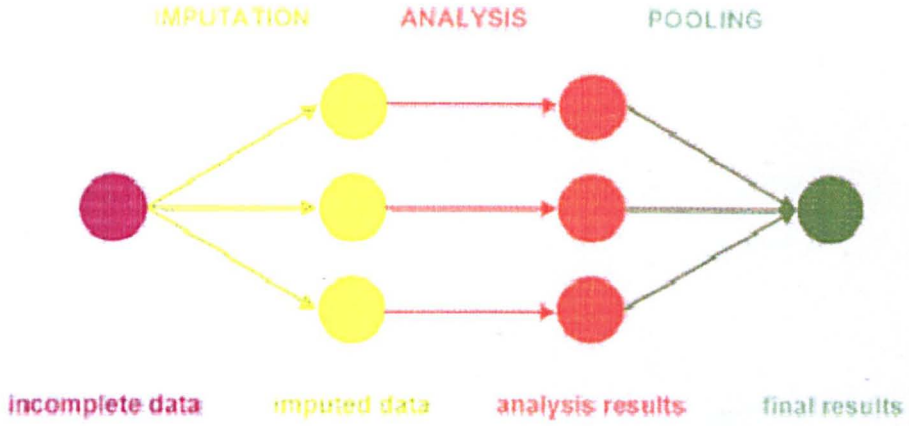
We can never determine whether data is MCAR, MAR or MNAR, but from analysis of our dataset we can never distinguish between MCAR and MAR. Most common statistical techniques assume that data are MAR.

Methodology

Multiple imputation imputes missing entries (Y_M), based on observed or non-missing entries (Y_O), by regressing the variable (Y) with missing data on the co-variables (Q) (e.g. age, morphology).[40,42] When there is more than one variable with missing data the method of 'chained equations' can be used whereby each variable with missing data is imputed using a regression model conditional on all other variables and is repeated for each variable with missing data.[27,43] Multiple imputation by chained equations is frequently used for imputation but another options are model-based methods (e.g. expectation-maximization algorithm)[44] or a weighted approach.[35] Model-based methods fit the missing data mechanism as part of the analysis model, rather than before the statistical analysis as occurs in chained equations. Model-based methods are complex, particularly for non-statisticians, and statistical software is less readily availible.[33]

Multiple imputation involves three steps; imputation, analysis and pooling of final results (Figure 4.2).

Figure 4.2: Multiple imputation steps



Source: van Burren S. Multiple Imputation Online. 2007. [42]

The imputation step predicts (Q_{MI}) the missing entries for each level (e.g. stage I, II, III, IV) of the variable based on a regression of the non-missing co-variables in the dataset (Y_o).

$$Q_{MI} = \mathrm{E}_{Y_M|Y_O}\ \mathrm{E}[\mathrm{Q}(\mathrm{Y}_\mathrm{O}, Y_M)] \tag{8}$$

For example multiple imputation of stage predicted the missing entries (Y_M) based on the distribution of explanatory variables (age, morphology, treatment, survival time) association with the non-missing entries for stage (Y_O). Imputation models should include all variables known to predict missingness including outcome variables (survival time), and all variables to be analysed in the final model should be included.[34] Imputation is repeated several times (k) using independent draws from the original dataset, resulting in k datasets with complete data for survival analysis and a set of k results pooled. The variance (Equation 9) for the final analysis will consist of a combination of the variance within each analysis (W) and between analysis variance (B). Between analyses variance is the additional variance due to the uncertainty surrounding imputed variables.

$$T = W + B * (1 + \frac{1}{k}) \tag{9}$$

If the assumptions for the model and the mechanism of missing data are correct, then resulting inferences will be statistically valid.[42]

For highly collinear variables conversion to logarithmic or orthoganal scales prior to multiple imputation avoids the variables being dropped from the model due to collinearity. Orthogonalising creates a set of variables using a modified Gram-Schmidt

procedure[45] which can be used for imputation and converted back after imputation with subsequent analysis conducted as usual.

Imputation accuracy increases with the number of co-variates used, and the number of imputations carried out. However, inappropriate choice of co-variates or exclusion of key co-variates in the imputation model can lead to bias in the final analysis while inclusion of unnecessary co-variates can led to over fitting and reduce precision.[24,34] On balance the risk of over fitting is less than that of bias, thus it is recommended to err on the side of caution and incorporate questionable co-variables.[34] The importance of including survival time and vital status has been demonstrated in the imputation models when dealing with longitudinal data.[27]

Multiple imputation by chained equations

Suppose that variables x_1, x_2, are incomplete, and $x_3,\ldots,x_k$ are fully observed, the method proceeds by :

1. Filling in each incomplete (x_1, x_2) variable by a starting value.
2. Discard the filled-in values from the x_1 leaving the original missing values.
3. An appropriate imputation model (linear regression, polytomous regression or logistic regression) is specified conditionally on all other variables (observed and imputed (if any) combined).
4. Regress x_1, on x_2, ..., x_k.
5. Replace missing values in x_1 by predicted values.
6. Repeat for x_2, and sequentially on other x's, (one iteration)
7. The same procedure is repeated for several (in this case 10) iterations. This generates one completed dataset.
8. For each completed dataset estimate relative survival $\hat{P}_j$ for each combination of relevant predictor variables and save the results to a file.
9. We then fit a multivariable regression using a generalized linear model with Poisson error[2] to estimate the excess hazard ratio of relative survival for colorectal cancer patients over the background mortality.

10. Combine estimates from completed datasets, to obtain the mean of the estimate (excess hazard ratio), and variance.

Analysis

The degree to which socioeconomic inequalities in survival could be explained by stage, comorbidity and other clinical and demographic factors was evaluated through the excess hazard ratio of death using data after imputation.

The method of estimating comorbidity and the most appropriate time window was first evaluated for use in subsequent analysis. The excess hazard of death within one year of diagnosis using original data (before imputation) was estimated for Ghali, Charlson, 'moderated' Charlson and Elixhauser comorbidity measures in order to determine the strength of association between each and one year survival. Charlson and Ghali comorbidity measures were found to be more strongly associated with the excess hazard of death at one year than the 'moderated' Charlson and Elixhauser measures. Multiple imputation was used to handle missing data for the Charlson and Ghali measures for each of the four time windows (i.e. multiple imputation was conducted eight times). The multiple imputation model will be described below and was consistent for both Charlson and Ghali measures (and each time window). After imputation comparisons of the excess hazard ratio of death were used to evaluate the Charlson and Ghali measures for each time window.

The multiple imputation included variables and interactions based on documented knowledge of cancer registry data collection system and previous research on variations for missing cancer registry data.[30,31,46] The associations of variables and missingness of data were analysed to support the assumption that the mechanism of missing data was MAR (see chapter 3). The imputation model included clinical factors (stage, grade, histology, comorbidity, colorectal cancer subsite), demographic factors (age group, socioeconomic status, sex) (see Table 6.8), treatment factors (surgery, chemotherapy, radiotherapy, surgeon volume, hospital volume) vital status and survival time. In order to include so many variables and decrease computation time each variable was categorised as outlined in Table 8.6. Interactions between follow-up time and each of stage, age and socioeconomic status were included because they were identified as non-proportional in analysis of the complete dataset.

The excess hazard of death was estimated using Poisson model in Generalized linear models within the multiple imputation software in STATA. Multiple imputation software (MIM) in STATA estimates the excess hazard ratio of death and variance (based on between and within imputation datasets). For each clinical and demographic variables the socioeconomic-specific excess hazard ratio of death was initially estimated (or the deprivation gap) at one year after diagnosis and at five years conditional on surviving the first year.

Summary generalized linear models were developed to describe the socioeconomic variations after adjusting for all relevant variables (end of each chapter 5 to 8). Each clinical, demographic and treatment variable was sequentially added to the generalized linear model and tested for significance, with each highly significant ($p<0.001$). Stage, age and deprivation were non-proportional over time. Ideally, the more advanced technique of splines[11,47,48] would have been used to take account of non-proportionality, but the software for the application of splines using imputed data was not yet available. Non-proportionality was instead accounted for in a step-wise function including interactions between follow-up time and each of stage, age and deprivation. Follow-up time was categorised into the first year after diagnosis and second to five years after diagnosis. The assumption of proportional excess hazards for the first year and second to five years after diagnosis may be reasonable, because the excess mortality is initially high then decreases dramatically during the first year since diagnosis, but remains fairly stable at a lower level afterwards. Each time-by-variable interaction was tested using the likelihood ratio test and was significant at $p<=0.001$.

Strategy

It is clear from previous studies of registry data,[28-31] and initial analysis of this dataset, that stage is not MCAR (Table 3.12). Determining whether stage is MAR or MNAR was not as simple, and required assessment of the mechanism underlying the missing data, based on associations with missing data, and knowledge of the potential reasons for missing data. Associations with missing data and the assumptions based on these will be detailed in Chapter 6.

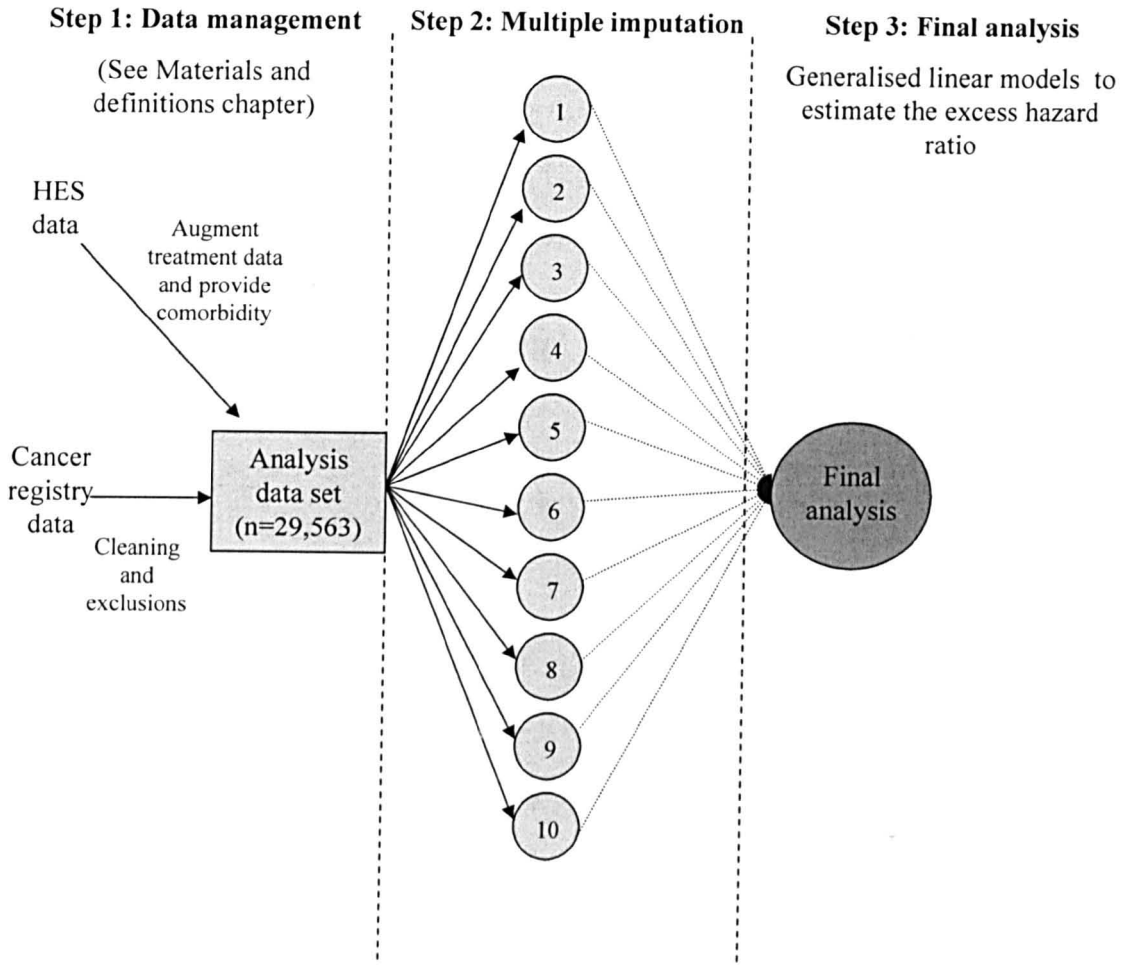
The aim of imputation was to estimate the underlying data, for stage, grade, morphology, comorbidity, surgery, chemotherapy, radiotherapy, hospital and surgeon volume of treatment, so that the degree of invalidity is decreased. Stage was incomplete for 39.5% of the available data, but other variables were recorded with high levels of

completeness, therefore developing a model for imputation of missing data for stage and other data (e.g. treatment) was the most effective method to incorporate all the data and avoid potential bias.

In order to estimate the influence of stage and treatment on socioeconomic inequalities missing data were imputed using multiple imputation techniques. The data after imputation were then used to estimate the excess mortality using deprivation-, region- and time-specific life tables to take into account differences in the underlying mortality. The expected excess mortality was estimated for combinations of variables to be studied (e.g. age, stage, comorbidity, treatment etc) and multivariable models estimated using generalized linear models using individual level data.

Analysis was done in four steps 1) data management 2) multiple imputation 3) final analysis with generalized linear models of the excess deaths (or excess mortality) (Figure 4.3).

Figure 4.3: Analysis and imputations steps



Step 1: Data management

The first step was data management, which was detailed in the Materials and definitions (chapter 3). Briefly, this step involved data cleaning, applying exclusions for the cancer registry data and adding treatment and comorbidity information from HES.

Step 2: Multiple imputation

Multiple imputation by chained equations[27] in STATA was used to recover missing data in covariates using Gibbs sampling.[49] Multiple imputation is an iterative technique, which deals with missing values when more than one variable is incomplete. The method assumes that a multivariate distribution exists, without specifying a specific form for it, and draws from it are generated by Gibbs sampling the conditional distributions. The imputation model included each incomplete variable (e.g. stage, Table 4.1), complete variables (e.g. age, year of diagnosis) and outcome (survival time, vital status). Imputation models were specified for each incomplete variable such as, logistic regression for binary variables (e.g. sex, vital status), normal linear regression for continuous variables (e.g. age in years) and ploytmous logistic regression for

categorical variables with more than two levels (e.g. stage). In this research it was not always clear when information was missing or did not occur (e.g. missing surgery, no surgery)

Cancer registries attempt to improve the completeness and accuracy of data for these variables by case-note extraction, linkage to external datasets (screening, specialist registration datasets, research), and case-note audits. All these approaches are routinely done at MCCR and NWCR. In order to ensure the dataset was complete, further linkage to hospital episode statistics was done. Even after linkage of cancer registry data and HES some variables were not known for some patients.

Every colorectal cancer patient must have a specific stage at diagnosis, tumour grade and histological tumour type, however comorbidity and treatment factors may be absent. For example, patients must have a stage ranging between I and IV, even if unrecorded, but the same is not true of treatment or comorbidity. For example, patients may have surgery, no surgery or have unrecorded surgery status (missing). Subsequently, the determination of whether a factor is missing is different for clinical factors and treatment factors (and comorbidity). Patients with unrecorded stage, grade and histology were imputed if there was no recorded stage, grade or histology. In contrast tumour records without comorbidity, surgery, chemotherapy, radiotherapy, hospital volume or surgeon volume may be a true record of the patient's experience (i.e. no chemotherapy, no comorbidity) and can not automatically be assumed to be missing.

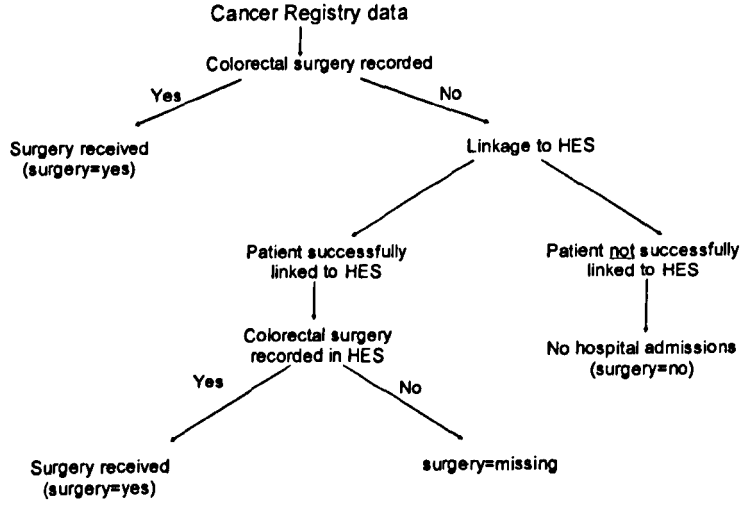
Table 4.1: Co-variates with missing data and percentage missing

Varible with missing data	%
Stage	39.5
Histology	11.6
Grade	25.0
Comorbidity	19.3
Surgery	8.9
Chemotherapy	63.9
Radiotherapy	19.6
Surgeon volume	21.6
Hospital volume	20.0

In the absence of actively recording if treatment or comorbidity is not present[11] it was necessary to make some assumptions about when treatment factors and comorbidity did not occur (e.g. no surgery, no comorbidity) or were missing (e.g. unknown surgery status, unknown comorbidity). These assumptions were developed based on data collection methods, completeness and accuracy of cancer registry and HES treatment data.

Linkage of colorectal cancer patient's in the cancer registry data to HES achieved a good linkage (82%, see chapter 3), unlinked patients with no registry record of surgery were assumed not to have had surgery. In the simplest situation patients had surgery recorded in the cancer registry (Figure 4.4). For patients without surgery recorded in the cancer registry, and for whom linkage to HES was obtained, surgery was assumed to be unknown (or missing) and was imputed. This assumption was made because individual inspection identified OPCS-4 codes that could be associated with colorectal cancer surgery for many of these patients (e.g. opening of the abdominal cavity, or anaesthesia) but no colorectal cancer surgery code. Additionally, in the earlier time periods HES was known to under record surgery. 67% of patients were recorded as having surgery in the cancer registry data. The addition of HES data improved the proportion of patients receiving surgery to 82% and imputation further increased the proportion of patients having surgery to 90%.

Figure 4.4: Surgery data and determination of missingness



[11] Active negative recording occurs when a non-occurrence is recorded (e.g. no surgery = 0). Any patients without positive or negative information recorded would be truly missing data.

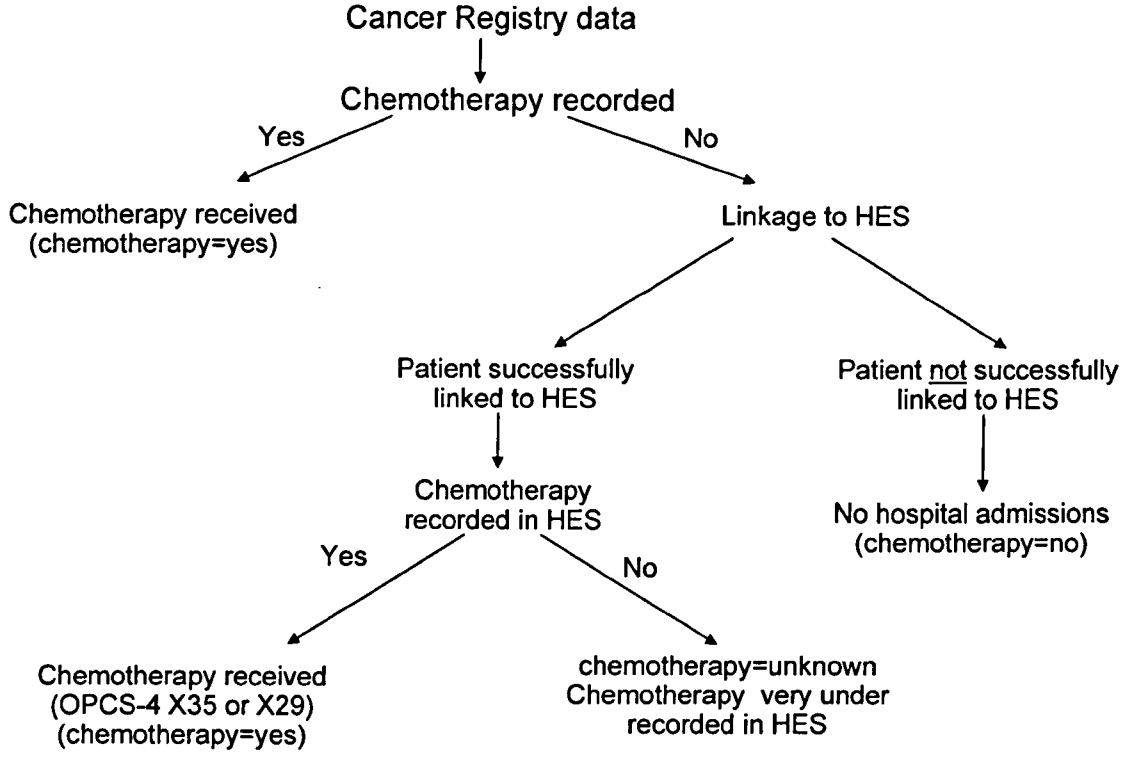
Hospital and surgeon volume was categorised based on the number of colorectal cancer surgeries conducted per year (see chapter 3). Patients who did not have surgery were assigned no surgeon volume and hospital volume (Table 4.2). Hospital and surgeon volume was imputed for patients who had surgery but missing data on hospital/surgeon volume, or who had missing surgery status. Inspection of individual surgical codes and comparison to cancer registry data appeared to show improvements in surgery coding between 1997 and 2004.

Table 4.2: Relation between surgery status and hospital volume and surgeon volume

	Hospital/Surgeon volume	
Surgery	**Yes**	**missing**
Yes	✓	Impute
No	-	None
missing	-	Impute

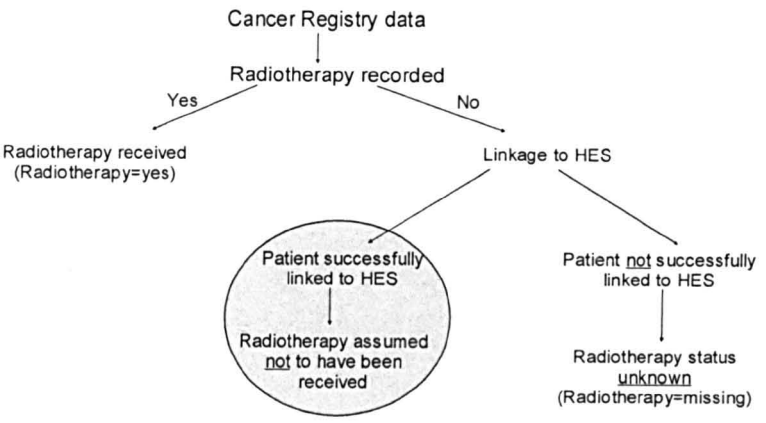
The determination of when chemotherapy data was missing followed a similar model to surgery data. Patients with chemotherapy recorded in either the cancer registry or HES data were assumed to have had chemotherapy, although this constituted a small proportion of patients (17.8%). Chemotherapy data is known to be under recorded in HES, because HES records procedures, such as chemotherapy received intravenously, but does not record chemotherapy received orally. Patients who were linked to HES but did not have chemotherapy data recorded in the cancer registry or HES were assumed to have missing chemotherapy data (Figure 4.5). Only patients without a record of chemotherapy in the cancer registry, and who were not linked to HES were assumed to have no chemotherapy. This method of assigning missingness might be considered conservative, however there are known biases in the data recorded in HES that must be taken into account. Hospital attendance and surgery is important for charging and measuring activity level. There is therefore a financial incentive to record attendance at hospital and it appears well recorded. Non-surgical treatment is less important for charging and measuring activity and is often not recorded (such as chemotherapy).

Figure 4.5: Chemotherapy data and determination of missingness



The method of assigning missingness for radiotherapy data was different to chemotherapy and surgery because i) the data in the cancer registry was accurate and complete and ii) there was no other source (HES does not record radiotherapy treatment). Radiotherapy treatment information was only available from the cancer registry, but is well recorded. However, HES should still have a hospital admission (in-patient or out-patient) for radiotherapy treatment. Each of the three radiotherapy centres in the North West provide highly complete radiotherapy information to the cancer registry. Patients were assumed not to have received radiotherapy if they had no record of radiotherapy and had no hospital admissions. Patients without radiotherapy treatment recorded but had no hospital admissions were assumed to be missing radiotherapy information.

Figure 4.6: Radiotherapy and determination of missingness



All three radiotherapy centres in the North West provide highly complete radiotherapy data to the cancer registry. Patients admitted or attending hospital for radiotherapy should have a hospital admission (although radiotherapy treatment would not specifically be recorded).

It was assumed any patient no recorded radiotherapy treatment in the cancer registry and without a hospital admission were missing radiotherapy data.

The level of comorbidity for each patient was estimated based on their previous hospital admissions and any previous cancer diagnosis for Ghali, Charlson, 'moderated' Charlson and Elixhauser comorbidity measures (see chapter 3). The comorbidity information for patients linked to HES was derived from the diagnosis fields recorded during hospital admission (see Table 3.4). Patients for whom cancer registry records could not be linked to HES were assumed to have no information with which to estimate comorbidity and were assumed to have missing data. Comorbidity levels for both Ghali and Charlson comorbidity measures for each of the four time windows were imputed in order to evaluate the measures (i.e. eight imputed data sets).

The multiple imputation model included the variables: age, sex, deprivation, comorbidity, stage, grade, histology, chemotherapy, radiotherapy, surgery, hospital volume and surgeon volume and the outcome variables of vital status and follow-up time. The completeness of variables to be imputed ranged from 37.5% for chemotherapy to 88% for morphological type (Table 4.1). Interaction terms were included for stage and follow-up time; age and follow-up time; deprivation and follow-up time; and comorbidity and age.

To avoid problems with small numbers and non-convergence, age and time were grouped. Age was grouped into 15 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84 and 85 to 99. Follow-up time was grouped into less than 6 months, 6 months up to 1 year and yearly intervals up to five years. Stage, age and comorbidity were highly collinear and

were orthoganised before imputation to avoid being dropped (due to non-convergence); they were reverted back before estimating survival and excess mortality.

Hospital and surgeon volume were both imputed conditionally on surgery status (both imputed and complete). This was achieved by including an interaction between the surgery flag (0/1) separately for hospital volume and surgeon volume, such that if surgery did not occur then surgeon volume and hospital volume were forced to zero. For example, for a given patient if it was imputed that no surgery occurred the patient must also have no hospital and surgeon volume. However if surgery occurred (known or imputed) then hospital and surgeon volume must be estimated (low, mid, high or very high).

Except when large proportions of data are missing, five to ten iterations have been deemed sufficient.[24,50] Ten iterations were used in this study.

Step 3: Multivariable analysis of excess hazard ratio of death

For each of the ten imputed datasets, excess mortality were estimated for each combination of relevant predictor variables with the results saved to 10 separate files. Excess mortality was calculated using the strs algorithm on individual data, as it allows the application of generalized linear models (GLM) of excess mortality[2] with a Poisson error structure as described in step 3. For the excess hazard of death, follow-up time was defined into a number of intervals. The follow-up interval structure was every three months for the first three years, then six monthly up to five years and yearly after five years.

Multiply-imputed software in STATA was used to analyse the imputed data because it enables analysis of imputed data using standard analysis such as multivariable GLM modelling.[43] Each dataset was analysed independently with the final estimate an average of the analyses for each dataset.[43] Standard errors were estimated as defined by Rubin[24] (Equation 9) by incorporating variation within and between datasets.

Treatment was then combined into one variable as previously outlined in the materials section (e.g. surgery only, surgery and chemotherapy,..no treatment).

To compare and evaluate comorbidity measures, the multiple imputation was used to estimate missing data for Charlson and Ghali scores for comorbid conditions occurring 18 to 6 months before diagnosis, the 6 months before diagnosis, in the first year after diagnosis and at any time (Figure 3.3).

Summary

The methods used to analyse colorectal cancer survival were complex but necessary to ensure the results were not biased by missing data. Relative survival is the gold standard method for analysing survival in population-based cancer registry data. When adjusting for multiple factors, Poisson models for excess mortality provide the most practical method to assess the impact and relationship of multiple variables. Population-based cancer registry data have high levels of completeness and accuracy for tumour details but even after HES is used to further improve data, treatment and staging data were incomplete. Multiple imputation was used to handle missing data, thus allowing analysis of relative survival or the excess hazard of death with a completed dataset.

Reference List

(1) Dickman PW, Hakulinen T. Population-based cancer survival analysis. Unpublished; 2006.

(2) Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Statistics in Medicine.* 2004; 23:51-64.

(3) Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association.* 1958; 53:457-481.

(4) Gail MH. Competing risks. In: Kotz S, Johnson NL, editors. *Encyclopedia of Statistical Sciences.* vol 2 ed. New York: Wiley, 1982, 75-81.

(5) Tsiatis AA. Completing risks. In: Armitage P, Colton T, editors. *Encyclopedia of Biostatisitcs.* vol 1 ed. Chichester: Wiley, 1998, 824-834.

(6) Estève J, Benhamou E, Raymond L. *Statistical methods in cancer research, volume IV. Descriptive epidemiology. (IARC Scientific Publications No. 128).* Lyon: IARC, 1994.

(7) Ederer F, Axtell LM, Cutler SJ. The relative survival rate: A statistical methodology. *National Cancer Institute Monograph.* 1961; 6:101-121.

(8) Breslow NE, Day NE. Statistical methods in cancer research: The design and analysis of cohort studies. Lyon: IARC Scientific Publications; 1987.

(9) Kasal J, Jovanovic Z, Clermont G, Weissfeld LA, Kaplan V, Watson RS, Angus DC. Comparison of Cox and Gray's survival models in severe sepsis. *Critical Care in Medicine.* 2004; 32:700-707.

(10) Berger U, Schäfer J, Ulm K. Dynamic Cox modelling based on fractional polynomials: time-variations in gastric cancer prognosis. *Statistics in Medicine.* 2003; 22:1163-1180.

(11) Giorgi R, Abrahamowicz M, Quantin C, Bolard P, Estève J, Gouvernet J, Faivre J. A relative survival regression model using B-spline functions to model non-proportional hazards. *Statistics in Medicine.* 2003; 22:2767-2784.

(12) Estève J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival: elements for further discussion. *Statistics in Medicine.* 1990; 9:529-538.

(13) Hakulinen T, Tenkanen L. Regression analysis of relative survival rates. *Applied Statistics.* 1987; 36:309-317.

(14) Remontet L, Bossard N, Belot A, Estève J, and the French network of cancer registries FRANCIM. An overall strategy based on regression models to estimate relative survival and model the effect of prognostic factors in cancer survival studies. *Statistics in Medicine.* 2007; 26:2214-2228.

(15) Brenner H. Up-to-date survival curves of children with cancer by period analysis. *British Journal of Cancer.* 2003; 88:1693-1697.

(16) Brenner H, Spix C. Time trend and period methods for retrospective time trend in long-term cancer patient survival rates. *British Journal of Cancer.* 2003; 89:1260-1265.

(17) Brenner H, Spix C. Combining cohort and period methods for retrospective time trend analysis of long-term cancer patient survival rates. *British Journal of Cancer.* 2003; 89:1260-1265.

(18) Brenner H, Arndt V. Period analysis of cancer patient survival in datasets from which the month of diagnosis has been removed. *European Journal of Cancer.* 2005; 41:438-444.

(19) Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer.* 2004; 78:2004-2010.

(20) Brenner H. Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis. *Lancet.* 2002; 360:1131-1135.

(21) Cronin K, Mariotto A, Scoppa S, Green D, Clegg L. *Differences between Brenner et al. and NCI methods for calculating period survival.* London: Statistical Research and Applications Branch, National Cancer Institute, 2003.

(22) Brenner H, Rachet B. Hybrid analysis for up-to-date long-term survival rates in cancer regsitries with delayed recording of incident cases. *European Journal of Cancer.* 2004; 40:2494-2501.

(23) Ewbank DC, Gomez de Leon JC, Stoto MA. A reducible four-parameter system of model life tables. *Population Studies.* 1983; 37:127.

(24) Rubin DB. Multiple imputation for nonresponse in surveys. 2nd ed. New York: John Whiley & Sons; 1987.

(25) Wood AM, White IR, Hillsdon M, Carpenter J. Comparison of imputation and modelling methods in the analysis of physical activity trial with missing outcomes. *International Journal of Epidemiology.* 2005; 34:89-99.

(26) Clark TG, Stewart ME, Altman DG, Gabra H, Smyth JF. A prognostic model for ovarian cancer. *British Journal of Cancer.* 2001; 85:944-952.

(27) van Burren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Statistics in Medicine.* 1999; 18:681-694.

(28) Adams J, White M, Forman D. Are there socioeconomic gradients in stage and grade of breast cancer at diagnosis? Cross sectional analysis of UK cancer registry data. *British Medical Journal.* 2004; 329:142-143.

(29) Thomson C.on behalf of the Quality Assurance Group of the UK Association of Cancer Registries. *Annual Performance Indicators Report, 2006.* Birmingham: UKACR, 2006.

(30) Jestin P, Påhlman L, Glimelius B, Gunnarsson U. Cancer staging and survival in colon cancer is dependent on the quality of the pathologists' specimen examination. *European Journal of Cancer.* 2005; 41:2071-2078.

(31) Adams J, White M, Forman D. Are there socioeconomic gradients in the quality of data held by registries? *Journal of Epidemiology and Community Health.* 2004; 58:1052-1053.

(32) Little RJA, Rubin DB. Statistical analysis with missing data. New York: John Wiley & Sons; 1987.

(33) Carpenter JKenward MG. *Missing data in randomised controlled trials - a practical guide.* London: National Health Service, National Centre for Research on Methodology, 2007.

(34) Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Statistical Methods in Medical Research.* 2007; 16:199-218.

(35) Carpenter J, Kenward MG, White IR. Sensitivity analysis after multiple imputation under missing at random: a weighting approach. *Statistical Methods in Medical Research.* 2007; 16:259-275.

(36) Schafer JL. Analysis of incomplete multivariate data. London: Chapman and Hall; 1997.

(37) Gentlemen JF, Will BP, Berkel H, Gaudette L, Berthelot JM. The development of staging data for use in the microsimulation of lung cancer. *Health Reports.* 1992; 4:251-268.

(38) Woods LM. International differences in breast cancer survival and 'cure' by social deprivation; a comparative study of England and Australia. PhD dissertation. London School of Hygiene and Tropical Medicine, 2006.

(39) Nur U, Rachet B, Parmar MKB, Sydes MR, Cooper N, Lepage C, Northover J, James R, Coleman MP, on behalf of the AXIS collaborators. No socioeconomic inequalities in colorectal cancer survival within a randomised clinical trial. *British Journal of Cancer.* 2008; 99:1923-1928.

(40) Researcher Development Initiative. Missing Data. 2007. Available from URL: www.lshtm.ac.uk/msu/missingdata/index.html

(41) Carpenter J, Kenward MG. Missing data. 2009. (cited 20 Apr. 2009) Available from URL: **www.missingdata.org.uk**

(42) van Burren S. Multiple Imputation Online. 2007. (cited 10 Feb. 2007) Available from URL: www.multiple-imputation.com

(43) Royston P. Multiple imputation of missing values. *Stata Journal.* 2004; 4:227-241.

(44) Dempster AP, Laird NM, Rubin DB. Maximum Likelihood from incomplete data via EM algorithm. *Journal of the Royal Statistical Society B.* 1977; 39:1-38.

(45) Golub GH, Van Loan CF. Matrix computations. 3rd ed. Baltimore: Johns Hopkins University Press; 1996.

(46) Green J, Watson J, Roche M, Beral V, Patnick J. Stage, grade, and morphology of tumours of the colon and rectum recorded in the Oxford Cancer Registry, 1995-2003. *British Journal of Cancer.* 2007; 96:140-142.

(47) Hess KR. Assessing time-by-covariate interactions in proportional hazards regression models using cubic spline functions. *Statistics in Medicine.* 1994; 13:1045-1062.

(48) Abrahamowicz M, MacKenzie T, Esdaile JM. Time-dependent hazard ratio: modelling and hypothesis testing with application in Lupus Nephritis. *Journal of the American Statistical Association.* 1996; 91:1432-1439.

(49) Geman S, Geman D. Stochastic relaxation, Gibbs distribution and Bayesian restoration of images. *IEEE Transactions on Pattern Analysis and Machine Intelligence.* 1984; 6:721-741.

(50) Rubin DB. Multiple imputation after 18+ years. *Journal of the American Statistical Association.* 1996; 91:473-490.

Chapter 5

Colorectal cancer survival and comorbidity: does the choice of comorbidity indicator matter?

Overview

Comorbidity, or illnesses other than the primary illness under treatment, is more common in patients who are older and of lower socioeconomic status.[1-3] Comorbid conditions may influence both the clinical appropriateness of a given treatment and its effectiveness, particularly for cancer patients who may need intensive surgery or prolonged chemo- or radiotherapy treatment.[4] Comorbidity measures are regularly recorded in clinical and audit studies using case-note review or patient assessment at diagnosis. Recording comorbidity for all patients in a population-based cancer registry is more challenging. Population-based cancer registry data include all patients, even those who are not eligible for active treatment because of late stage or severe comorbidity, and who are normally excluded from clinical or audit studies. Clinical trials, by contrast, are often restricted to patients meeting strict criteria, usually under 75 years of age and in good overall health.[5]

Aim

This chapter contains an evaluation of various approaches to assigning overall comorbidity scores that incorporate the number and severity of comorbid conditions to cancer patients in population-based data. Hospital Episode Statistics (HES) data[6] were used to estimate the variation in one-year survival associated with different levels of the Charlson, Elixhauser and Ghali comorbidity measures. A 'moderated Charlson' measure was developed that included other conditions known to be contra-indicators for surgery and was compared to the other comorbidity measures. Comorbidity scores for each measure were categorised into four levels (none, 1, 2 and 3 or more). Conditions diagnosed at or around the time of cancer diagnosis may have been initiated or increased in severity by the cancer and/or its treatment. The impact on survival of comorbid conditions was therefore assess in relation to various time windows around the cancer diagnosis and in order to elucidate the best method of measuring comorbidity as a prognostic factor in cancer survival analysis. The four time windows evaluated were; 18 months to 6 months before cancer diagnosis, 6 months before cancer diagnosis, the first 12 months after cancer diagnosis and any comorbidity between the financial years of 1996/07 and 2005/06.

For the Charlson and Ghali measures multiple imputation was used to estimate the level of comorbidity when the underlying score was missing. Evaluation of the multiple imputation model and its impact on the comorbidity levels associated with other variables and survival will be evaluated in Chapter 6. The imputation model used for the Charlson measure at 18 months to 6 months before diagnosis was also applied to the Charlson and Ghali comorbidity measures for each time window. The Elixhauser and moderated Charlson measures were evaluated as only weak measures of comorbidity analysis, and were not no imputation were done for these measures.

The analysis presented in this chapter will mainly be based on data after imputation, unless otherwise specified.

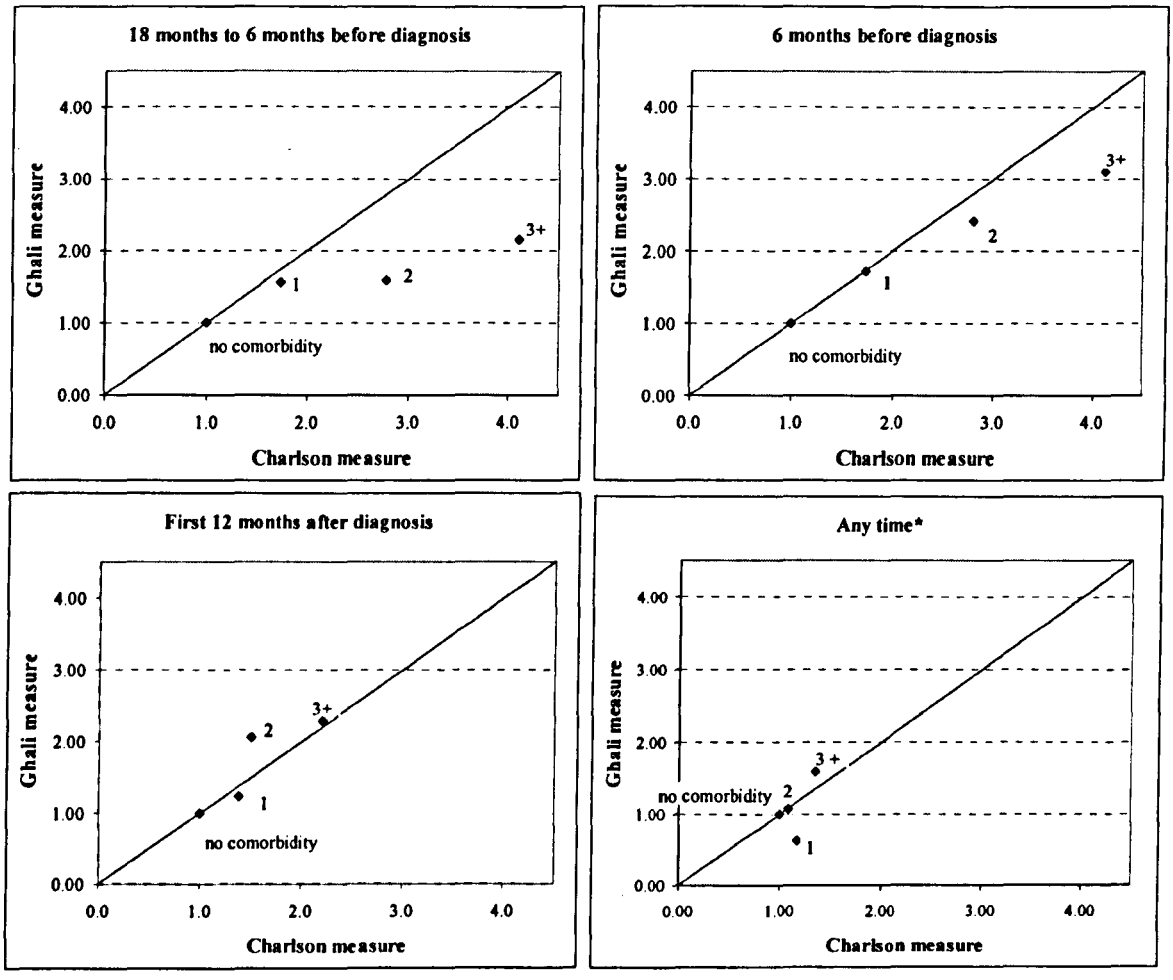
Choice of index and time window

Comorbid conditions may increase in severity due to the presence of colorectal cancer and the diagnostic procedures and treatment procedures for colorectal cancer. The association of the timing (or 'time window') of comorbid conditions in relation to the diagnosis of colorectal cancer was evaluated based on comorbid conditions recorded in hospital admissions at: any time during the financial years 1996/97 to 2005/06; in the 18 to 6 months before colorectal cancer diagnosis; 6 months before colorectal cancer diagnosis; or the first year after colorectal cancer diagnosis. The excess hazard of death for each level of the Charlson and Ghali measure for each of the four time windows were compared. For most time windows the Charlson and Ghali measures were associated with a similar excess hazard ratio of death for each level of comorbidity (Table 5.1, Figure 5.1). The excess hazard ratio was higher for Charlson measure in the 18 to 6 months before diagnosis (4.1, 95% CI 3.8-4.5) than with the Ghali measure (2.2 95% CI 1.8-2.6). In the six months before a colorectal cancer diagnosis the Charlson comorbidity measure were consistently higher than Ghali measure. In the year following a colorectal cancer diagnosis and any time between 1996/07 and 2005/6 the Ghali measure was marginally higher than the Charlson measure, although this was not significant. This pattern remained at five years after diagnosis although the association was moderated because the impact of comorbidity mainly occurred in the first year after diagnosis (Appendix 5.1). Comorbidity diagnosed at any time was not associated with an excess hazard except for patients with 3 or more for both Charlson and Ghali measures. There was only a weak association between the excess hazard ratio for increasing levels of comorbidity in the Elixhauser and moderated Charlson measures (Appendix 5.2).

Table 5.1: Distribution of patients (%) and excess hazard ratio of death within one year diagnosis by level of comorbidity (Charlson and Ghali comorbidity measures) and time window within which comorbidity was recorded: colorectal cancer patients diagnosed 1997-2004, North West of England (after imputation)

	Charlson				Ghali			
		EHR				EHR		
	% of		95% CI		% of		95% CI	
level	patients		lower	upper	patients		lower	upper
18 months to 6 months before diagnosis								
0	77.9	1.00	-	-	97.8	1.00	-	-
1	5.2	1.73	1.54	1.93	0.4	1.56	1.12	2.18
2	8.9	2.78	2.56	3.02	0.9	1.60	1.30	1.95
3+	7.9	4.11	3.77	4.48	0.9	2.15	1.80	2.57
6 months before diagnosis								
0	65.6	1.00	-	-	89.6	1.00	-	-
1	13.1	1.74	1.51	1.99	1.7	1.72	1.44	2.05
2	9.0	2.80	2.53	3.11	2.6	2.41	2.09	2.77
3+	12.5	4.12	3.71	4.59	6.1	3.11	2.83	3.41
First 12 months after diagnosis								
0	65.5	1.00	-	-	88.6	1.00	-	-
1	12.9	1.38	1.28	1.48	1.6	1.23	1.02	1.49
2	9.2	1.49	1.33	1.66	3.2	2.06	1.80	2.34
3+	12.4	2.20	1.87	2.59	6.6	2.29	2.08	2.51
Any time								
0	49.5	1.00	-	-	78.2	1.00	-	-
1	12.8	1.17	1.09	1.25	9.0	0.62	0.46	0.83
2	11.4	1.09	1.01	1.18	3.8	1.07	0.94	1.23
3+	26.3	1.35	1.26	1.44	17.1	1.59	1.49	1.70

Figure 5.1: Direct comparison of the excess hazard ratio of death at one year after diagnosis for colorectal cancer by the four levels of Charlson and Ghali measures and time window within which comorbidity was recorded: colorectal cancer patients diagnosed 1997-2004, North West of England (imputed) (reference = no comorbidity score)



*Patients diagnosed with comorbidity between 1997/06 and 2005/06

Two moderations to the Charlson comorbidity measure were evaluated for their impact on survival patterns. The moderated Charlson included the standard 16 Charlson comorbid conditions plus hypertension, ischaemic heart disease, pulmonary embolism and obesity each with of the additional comorbid conditions given a severity weight of one. Another moderation to the Charlson measure obtained previous cancer diagnosis from hospital admissions rather than from cancer registry data. The addition of hypertension, ischaemic heart disease, pulmonary embolism and obesity to Charlson comorbidity measure identified substantially more patients with comorbidity but had a weak association with survival (Appendix 5.2). Hypertension and ischaemic heart disease occurred in a large proportion of patients but were not significantly associated with an excess hazard of death (Table 5.4). Obesity identified very few patients (n=113,

0.4%). Of the four additional diagnoses only pulmonary embolism (n=311, 1.1%) diagnosed at any time was significantly associated with the excess hazard of death (1.28 95% CI 1.08-1.52).

The Charlson and Ghali measures had similar excess relative survival for most time windows, while the Elixhauser and modified Charlson measures were weakly associated with survival (Appendix 5.2). The weak association of the modified Charlson measure with survival was mainly due to the inclusion of hypertension which was associated with a large number of patients but an apparently protective effect (excess hazard ratio 0.64).

The comorbidity scores in all time windows were highly skewed. Most patients had no recorded comorbidity score at any time (Charlson: 68.5%, modified Charlson: 65.9%, Ghali: 85.9% Elixhauser: 55.5%). A small proportion of patients had high levels of comorbidity (Table 5.2, Appendix 5.2). The time window identifying the most comorbidity was consistent for all methods and occurred in decreasing order in the comorbidity window of anytime, during treatment, 6 months prior to diagnosis and at 18 months to 6 months prior to diagnosis, respectively.

Table 5.2: Distribution of weighted comorbidity scores by time window: Charlson comorbidity measure: colorectal cancer patients diagnosed 1997-2004, North West of England

	Any time		18 months to 6 months before diagnosis		6 months before to diagnosis		First 12 months after diagnosis	
Comorbidity score	No.	%	No.	%	No.	%	No.	%
0	20,248	68.5	28,244	95.5	26,076	88.2	25,625	86.7
1	4,523	15.3	833	2.8	2,552	8.6	2,742	9.3
2	3,095	10.5	403	1.4	705	2.4	912	3.1
3	1,055	3.6	66	0.2	181	0.6	216	0.7
4	385	1.3	16	0.1	42	0.1	53	0.2
5	156	0.5	3	0.0	8	0.0	8	0.0
6	56	0.2			0	0.0	3	0.0
7	19	0.1			1	0.0	0	0.0
8	18	0.1					6	0.0
9	8	0.0						
10	0	0.0						
11	2	0.0						

Linkage quality

Linkage of HES data to cancer registry data obtained for this study was 82%, which was consistent with linkages in other registry-based studies in London and South West England (63%),[7] teenagers and young adults (86%),[8] and rectal cancer patients

undergoing abdominoperineal excision (92%).[9] Patients whose cancer registry data could not be linked to a HES record included those without any prior hospital admission and with no comorbid conditions, patients with a hospital admission but no recorded comorbidity (missing in HES) and those treated outside of the NHS. Patients that could not be linked to HES data were significantly more likely to have colon cancer (than rectal cancer), no treatment (rather than any other treatment), to be aged over 75 at diagnosis, and to be diagnosed at an advanced stage (data not shown).

Patients for whom cancer registry data could not be linked to HES may be systematically different with regards to survival and/or comorbidity than patients for whom a cancer registry to HES linkage was obtained. Patients with no hospital admissions may include patient who i) 'truly' have a comorbidity that is well managed (hence no hospital admissions), ii) have no comorbid conditions or iii) hospital admission data may be missing from HES. The impact of these scenarios on the excess hazard ratio of death for each level of the Charlson measure (at 18 to 6 months before diagnosis) were evaluated by excluding patients without a hospital admission, assuming patients not linked to HES had no comorbidity (0) and assuming patients not linked to HES had the highest level of comorbidity (3+). These three scenarios showed no significant difference in the excess hazard ratio at each comorbidity level, although limiting the estimates to patients linked to HES increased the excess hazard for scores 1 and 2 compared to the other estimates (Table 5.3). The impact of assuming patients that were not linked to hospital admission data had a Charlson comorbidity measure level of 3 or more being a biased toward higher comorbidity was evaluated by assuming they had higher levels of comorbidity (3 or more), increased the excess hazard ratio of death moderately and non-significantly to 2.92 (95% CI 2.79-3.05) for patients with a comorbidity level of 3 or more.

Table 5.3: Sensitivity analysis for excess hazard ratio of death for Charlson comorbidity measure at 18 to 6 months before diagnosis: colorectal cancer patients diagnosed 1997-2004, North West of England

	Patients for whom cancer registry record and HES data were linked (n=23,868)			All patients, with patients not linked to HES assumed to have comorbidity level 0 (n=29,563)			All patients, with patients not linked to HES assumed to have comorbidity level 3+ (n=29,563)		
	excess hazard ratio	95% CI		excess hazard ratio	95% CI		excess hazard ratio	95% CI	
level		lower	upper		lower	upper		lower	upper
0	1.00	-	-	1.00	-	-	1.00	-	-
1	1.46	1.25	1.72	1.32	1.16	1.50	1.32	1.16	1.50
2	1.47	1.15	1.87	1.38	1.16	1.64	1.38	1.16	1.64
3+	2.83	1.96	4.08	2.85	2.12	3.83	2.92	2.79	3.05

Despite the lack of significant difference in the excess hazard of death between the three scenarios patients that did not link with HES were assumed to have missing data and multiple imputation was used to estimate the comorbidity level in the Charlson comorbidity measure at 18 to 6 months before diagnosis. Imputed estimates of the excess hazard ratio of death for patients with a comorbidity level of 3 or more were slightly higher (3.2 95% CI 2.6-3.9) than all of the scenarios evaluated in the sensitivity analysis. Multiple imputation will be evaluated in Chapter 6 for all clinical and demographic variables.

Individual comorbid conditions

Among colorectal cancer patients diagnosed with between 1997 and 2004 in the North West the most common of the 17 conditions which make up the Charlson comorbidity measure (diagnosed at any time between the financial year 1996/97 and 2005/06) were chronic pulmonary disease (n=2,338, 7.9%), prior invasive malignancy (C00-C97 excl C44, n=1,788, 6.0%) and congestive heart failure (n=1,086, 3.7%) (Table 5.4). Nine conditions were associated with an excess hazard ratio of death above 1.0 (reference is no comorbidity). Due to small numbers individual comorbid conditions were analysed regardless of whether they occurred pre- or post-operatively. Only six conditions were significantly associated with an increased excess hazard ratio of death (congestive heart failure, cerebrovascular disease, dementia, hemi/paraplegia, renal disease, moderate/severe liver disease) and three significantly protective (previous malignancy, mild liver disease, rheumatic disease). Liver disease[1] was strongly associated with an excess hazard ratio of death (3.72 95% CI 1.90-7.30) however there were only 10 patients with recorded liver disease. Liver disease was strongly associated with an

[1] Moderate/severe liver disease (ICD-10 I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7), Liver metastasis is excluded.

excess hazard ratio of death (3.72 95% CI 1.90-7.30) however there were only 10 patients with recorded liver disease. Liver disease did not include metastatic liver cancer (C76-C80). It is plausible that some patients with this comorbid condition were diagnosed prior to diagnosing late stage colorectal cancer with liver metastasis thus explaining the poor prognosis in these patients. Congestive heart failure occurred in a large number of patients and predicted a 53% excess mortality. Only one patient had an HIV/AIDS diagnosis so this could not be evaluated as an individual comorbid condition but was included in the overall measures with a weight of six.

Table 5.4: Number (%) and excess hazard ratio of death at one year, for comorbid conditions included in the Charlson and modified Charlson measure at any time: colorectal cancer patients diagnosed 1997-2004, North West of England

Weight	Comorbidity	Patients†	Relative frequency	Excess hazard ratio	95% CI lower	95% CI upper	
1	Myocardial infarction	780	2.6	1.04	0.92	1.17	
1	Congestive heart failure	1,086	3.7	1.53	1.40	1.67	*
1	Peripheral vascular disease	498	1.7	0.88	0.75	1.04	
1	Cerebrovascular disease	867	2.9	1.19	1.07	1.33	*
1	Dementia	295	1.0	1.22	1.01	1.46	*
1	Chronic pulmonary disease	2,338	7.9	0.95	0.88	1.02	
1	Rheumatic disease	232	0.8	0.72	0.55	0.95	*
1	Peptic ulcer disease	468	1.6	0.92	0.78	1.09	
1	Mild liver disease	188	0.6	0.66	0.48	0.91	
1	Diabetes without chronic complication	797	2.7	0.73	0.63	8.84	
2	Diabetes with chronic complication	46	0.2	0.98	0.57	1.69	
2	Hemiplegia or paraplegia	234	0.8	1.42	1.18	1.71	*
2	Renal disease	470	1.6	1.18	1.02	1.37	*
3	Moderate or severe liver disease	10	<0.1	3.72	1.90	7.30	*
3	Any malignancy‡	1,788	6.0	0.73	0.66	0.81	*
6	Other metastatic solid tumour	15	0.1	1.44	0.32	6.39	
	Additions:						
1	Hypertension	5,902	20.0	0.64	0.60	0.68	*
1	Ischaemic heart disease	2,106	7.1	0.96	0.89	1.04	
1	Pulmonary embolism	311	1.1	1.28	1.08	1.52	*
1	Obesity	113	0.4	0.76	0.53	1.10	

* p-value<0.05

†Some patients will have more than one type of comorbidity and are included in each category

‡ Excluding benign tumours and non-melanoma skin cancer (C44), only first colorectal diagnosis included.

Hypertension, ischaemic heart disease, pulmonary embolism and obesity were evaluated as potential additions to the Charlson measure (or 'modified Charlson'), because they are potential contra-indications for some cancer treatment as well as increasing the overall risk of mortality. Patients with ischaemic heart disease should not receive some chemotherapy regimes (particularly 5FU) because of the cardiotoxicity. The modified Charlson measure did not improve the association between each level of comorbidity and the excess hazard of death, compared to the standard Charlson measure. Hypertension (n=5,902), ischaemic heart disease (n=2,106), pulmonary embolism (n=311) and obesity (n=113) occurred in 20.0%, 7.1%, 1.1%, and 0.4% of patients, respectively. Pulmonary embolism (1.28, 95% CI 1.08-1.52) was significantly associated with excess mortality while ischaemic heart disease (0.96, 95% CI 0.89-1.04), and obesity (0.76, 95% CI 0.53-1.10) were not. There was a significantly lower excess hazard associated with hypertension as a comorbidity (0.64, 95% CI 0.60-0.68).

Distribution of comorbidity

Higher levels of comorbidity are known to be associated with some clinical and demographic factors. The Charlson comorbidity measure for comorbid conditions

diagnosed between 18 and 6 months before diagnosis was used to evaluate clinical and demographic variations in the proportion of patients with each comorbidity level and the odds ratio for any comorbidity (compared to none). Comorbid conditions occurring in the time window of 18 to 6 months before colorectal cancer diagnosis were evaluated because this time window was the least likely to include the colorectal cancer diagnosis or treatment procedures. The prevalence (and adjusted odds ratio) of comorbidity at 18 to 6 months before diagnosis, was higher for patients aged over 55 at diagnosis, for more deprived and for those treated non-surgically. Increasing age was strongly associated with increasing levels of comorbidity increasing from 7.0% for patients aged 15-44 to 26.2% for patients 85-99 (Table 5.5). Women had a higher levels of comorbidity than men but were diagnosed at an older age than men (men 69.2 years, women 72.0 years). Women had apparently lower comorbidity levels than men after adjustment for clinical and demographic factors.

Deprived patients were more likely to have a comorbidity recorded than affluent patients (14.8% and 11.8%, respectively). Comorbidity was significantly higher in the three most deprived groups before adjustment comorbidity was only significant in the most deprived group after adjustment for age, subsite, diagnosis year stage and treatment.

The prevalence of comorbidity among colorectal cancer patients appears stable between 1999 and 2003, but is lower at the beginning of the study period probably because of artefact in the collection of HES data (1997, 1998). The collection and compilation of HES was refined and improved from the financial year 1996/97 with continued improvement over time. This reorganisation and further refinement of HES likely explains the lower comorbidity in 1997 to 1999. This is further supported by the lower levels of less severe comorbid conditions (level 1) recorded in 1997 and 1998 (possibly 1999) which might be expected to improve as data collection processes were refined. Patients diagnosed in 1997 would also have a shorted time period within which comorbid conditions could be recorded (only 1996/97 financial year) with this having a differential impact on less severe comorbid conditions.

Patients diagnosed with colon cancer had a higher prevalence of comorbidity than rectosigmoid or rectal cancer patients. The higher levels of comorbidity for colon cancer patients may be associated with the older age diagnosis for colon cancer patients, with

43.1% of patients over age 75 compared to 35.2% and 36.3% for rectosigmoid and rectal cancer, respectively. Before adjustment for clinical and demographic variables, cancers of the rectum or rectosigmoid were associated with a significantly lower level of comorbidity at 18 to 6 months than colon cancer patients but these differences were fully explained after adjustment for age, year of diagnosis, deprivation, stage and treatment.

Increasing levels of Charlson comorbidity at 18 to 6 months before diagnosis were strongly associated with advanced stage, rising from 7.1% of patients in stage I to 17.5% in stage IV. Patients in with stage IV colorectal cancer also had a high proportion of patients with level two (8.4%) and three or more (6.9%) comorbidity. Advanced stage at diagnosis (IV) was significant association with increasing comorbidity measures at 18 to 6 months.

Patients receiving only chemotherapy and/or radiotherapy had significantly higher levels of comorbidity than surgical patients. Variations in treatment regime and associations with clinical and demographic variables, including comorbidity, will be examined in detail in Chapter 7.

Table 5.5: Distribution (%) of Charlson comorbidity measure at 18 to 6 months before diagnosis and odds ratio for any comorbidity (baseline = no comorbidity) by clinical and demographic variables (imputed): colorectal cancer patients diagnosed 1997-2004, North West of England

	level of the Charlson comorbidity measure				Odds ratio		Odds ratio	
	zero	1	2	3+	(unadjusted)		(adjusted)†	
Gender								
Men	87.1	4.0	1.1	3.8	1.00		1.00	
Women	85.9	4.0	6.0	4.2	1.11	*	0.72	*
Age grouping								
15 to 44	93.0	1.9	3.7	1.2	1.00		1.00	
45 to 54	93.8	1.9	3.2	1.1	0.90		1.22	
55 to 64	90.8	2.9	4.3	2.1	1.40	*	1.97	*
65 to 74	89.1	3.6	4.6	2.8	1.68	*	2.51	*
75 to 84	83.3	5.1	6.5	5.1	2.74	*	3.32	*
85 to 99	73.8	6.1	9.6	10.7	4.86	*	3.94	*
Subsite (ICD-10)								
Colon (C18)	85.4	4.3	5.9	4.4	1.00		1.00	
Rectosigmoid (C19)	89.8	3.7	4.1	2.4	0.66	*	0.94	
Rectum (C20)	88.1	3.5	4.9	3.6	0.79	*	0.92	
Morphological type								
Adenocarcinoma	86.4	4.0	5.5	4.0	1.00			
Mucinous and serous	88.5	3.6	4.5	3.3	0.82	*		
Other	77.1	5.4	10.6	6.9	1.88	*		
Grade								
I	87.7	4.1	5.0	3.2	1.00			
II	87.0	3.9	5.2	3.9	1.06			
III	82.8	4.5	7.2	5.5	1.48	*		
IV	85.2	2.2	7.0	5.6	1.21			
Year of diagnosis								
1997	89.4	1.4	5.2	4.0	0.66	*	0.39	*
1998	87.9	3.5	4.8	3.8	0.77	*	0.74	*
1999	86.7	4.3	5.2	3.8	0.85	*	0.85	
2000	86.2	4.5	5.6	3.8	0.90		0.92	
2001	84.8	5.2	5.9	4.1	1.00		1.00	
2002	84.4	5.3	6.0	4.3	1.03		0.98	
2003	84.7	5.1	6.0	4.3	1.01		1.03	
2004	88.2	2.8	5.1	3.9	0.74	*	0.55	*
Deprivation group								
Affluent-1	88.2	3.5	5.2	3.1	1.00		1.00	
2	87.7	3.6	5.2	3.5	1.04		0.98	
3	86.6	3.7	5.8	3.5	1.15	*	1.08	
4	86.2	4.5	5.1	4.2	1.20	*	1.21	
Deprived-5	85.2	4.3	5.8	4.7	1.30	*	1.30	*
Stage								
I	93.9	3.2	2.3	0.7	1.00			
II	93.3	3.5	2.3	0.9	1.11			
III	94.1	3.1	2.0	0.8	0.97			
IV	80.5	4.2	8.4	6.9	3.74	*		
Treatment								
surgery only	94.9	3.6	1.3	0.3	1.00			
surgery and chemo	95.5	3.2	1.1	0.2	0.88		1.00	
surgery and radiotherapy	97.6	1.9	0.3	0.2	0.41		0.48	
surgery and chemoradiotherapy	98.0	1.7	0.3	0.1	0.39	*	0.50	*
chemotherapy only	17.5	17.9	45.5	19.1	88.20	*	133.15	*
radiotherapy only	47.2	17.0	25.5	10.4	20.75	*	24.70	*
chemoradiotherapy	42.1	16.9	29.4	11.6	25.46	*	38.1	*
no treatment	11.1	9.9	41.6	37.5	149.40	*	172.16	*
	86.5	4.0	5.5	4.0				

* Significant at p-value <=0.05

† adjusted for age group, deprivation, subsite, diagnosis year and treatment, excluding the variable being studied

Comorbidity and survival

Stage and age both substantially moderated the excess hazard ratio of death within one year of diagnosis for each level of the Charlson comorbidity measure at 18 to 6 months before diagnosis. Stage had a much weaker effect on the excess hazard for each level of the Ghali comorbidity measure (Table 5.6). Adjustment for deprivation had little impact on the excess hazard ratio of death for either Charlson or Ghali measures. Adjustment for treatment fully explained the excess hazard of death for each level of the comorbidity for both the Charlson and Ghali measures (not shown) highlighting the impact of comorbidity on treatment eligibility and the further validating association between the Charlson and Ghali measures with survival and treatment. Treatment was not included in the final adjusted model because stage, comorbidity and other clinical factors were predictors of treatment; thus treatment was on the causal pathway between these factors and outcome.

Increasing levels of the comorbidity at 18 to 6 months before colorectal cancer diagnosis were still associated with excess mortality at five years after diagnosis regardless of whether the Charlson or Ghali comorbidity measure was used (Appendix 5.3). The pattern was similar to that at one year after diagnosis, but moderated. The moderating impact of treatment on the excess hazard for each level of comorbidity was also weaker at five years after diagnosis than at one year.

Table 5.6: Excess hazard ratio for death at one year and for Charlson and Ghali comorbidity measures at 18 to 6 months, adjusted for age, stage, deprivation and treatment (imputed): colorectal cancer patients diagnosed 1997-2004, North West of England

		Charlson measure			Ghali measure		
		EHR			EHR		
			95% CI			95% CI	
level	Adjusted for		lower	upper		lower	upper
0		1.00	-	-	1.00	-	-
1	follow-up	1.73	1.54	1.93	1.56	1.12	2.18
2		2.78	2.56	3.02	1.60	1.30	1.95
3+		4.11	3.77	4.48	2.15	1.80	2.57
0	Age and follow-up	1.00	-	-	1.00	-	-
1		1.52	1.36	1.69	1.41	1.02	1.94
2		2.47	2.28	2.67	1.36	1.12	1.65
3+		3.25	2.99	3.53	1.60	1.35	1.90
0		1.00	-	-	1.00	-	-
1	Stage and follow-up	1.68	1.48	1.90	1.68	1.16	2.42
2		2.34	2.13	2.57	1.53	1.23	1.92
3+		3.18	2.88	3.53	2.20	1.81	2.68
0		1.00	-	-	1.00	-	-
1	Deprivation and follow-up	1.70	1.52	1.89	1.53	1.11	2.13
2		2.77	2.56	3.00	1.54	1.25	1.87
3+		4.04	3.72	4.39	2.08	1.75	2.48
0	Age, stage, deprivation, and follow-up	1.00	-	-	1.00	-	-
1		1.44	1.27	1.62	1.40	1.02	1.91
2		2.03	1.86	2.22	1.33	1.09	1.61
3+		2.45	2.22	2.70	1.57	1.32	1.85

Summary

Increasing levels of the comorbidity, particularly in the 18 months to 6 months before diagnosis of the colorectal cancer diagnosis were strongly associated with increasing excess hazard ratio of death within he first year after colorectal cancer diagnosis. This time window for comorbidity would be expected to exclude illnesses that may either have increased in severity or were due to a complication of colorectal cancer diagnosis or treatment. The Charlson comorbidity measure has been widely used and validated, but no other studies have assessed the time window of comorbid conditions in relation to cancer diagnosis (or other diseases). Increasing levels of comorbidity were associated with increasing age, increasing deprivation and more advanced stage at diagnosis. Even after adjusting for clinical and demographic factors, comorbidity, stage and age were the strongest predictors of excess mortality.

The estimated prevalence of previous cancers obtained from registry data was consistent with other studies,[1,2] but obtaining evidence of a presumptive previous cancer diagnosis from HES data greatly overestimated the prevalence. HES data may include suspected cancer, where results of diagnostic procedures are still pending, thus overestimating the true prevalence (e.g. suspected stomach later determined to be colorectal). Hospital administrative databases undoubtedly under-estimate the frequency of diseases which would not normally require hospital treatment, such as diabetes without complications, and other common chronic conditions, such as obesity, may also be under-recorded. The use of hospital admissions for estimating comorbidity will result in some degree of residual confounding, due to under-ascertainment of comorbid conditions. Despite this, HES and cancer registry data remain a good source of comorbid conditions from which to construct comorbidity measures.

For simplicity, in the analyses a single measure of comorbidity was selected. For the remainder of this thesis the Charlson comorbidity measure for illnesses diagnosed between 18 and 6 months before a colorectal cancer diagnosis will be used, with previous cancer diagnosis obtained from cancer registry information.

(1) Schrijvers C, Coebergh J, Mackenbach JP. Socioeconomic status and comorbidity among newly diagnosed cancer patients. *Cancer.* 1997; 80:1482-1488.

(2) De Marco MF, Janssen-Heijnen MLG, van der Heijden LH, Coebergh JWW. Comorbidity and colorectal cancer according to subsite and stage: a population-based study. *European Journal of Cancer.* 2000; 36:95-99.

(3) Gross CP, McAvay GJ, Krumholz HM, Paltiel AD, Bhasin D, Tinetti ME. The effect of age and chronic illness on life expectancy after a diagnosis of colorectal cancer: implications for screening. *Annals of Internal Medicine.* 2006; 145:646-654.

(4) Stukenborg GJ, Wagner DP, Connors AF. Comparison of the performance of two comorbidity measures, with and without information from prior hospitalizations. *Medical Care.* 2001; 39:727-739.

(5) Golfinopoulos V, Pentheroudakis G, Pavlidis N. Treatment of colorectal cancer in the elderly: a review of the literature. *Cancer Treatment Reviews.* 2006; 32:1-8.

(6) The information centre. HESonline. 2008. (cited 2 May 2008) Available from URL: www.hesonline.nhs.uk

(7) Jack RH, Davies EA, Møller H. Testis and prostate cancer incidence in ethnic groups in South East England. *International Journal of Andrology.* 2007; 30:215-221.

(8) Moran A, O'Hara C. UK database for teenagers and young adults with cancer. Shack L, editor. 2008. 9-6-2008.

(9) Morris E, Quirke P, Thomas JD, Fairley L, Cottier B, Forman D. Unacceptable variation in abdominoperineal excision rates for rectal cancer: time to intervene? *Gut.* 2008.

Appendix 5.1: Distribution of patients (%) and excess hazard ratio of death within five years of diagnosis by level of comorbidity (Charlson and Ghali comorbidity measures) and time window within which comorbidity was recorded: colorectal cancer patients diagnosed 1997-2004, North West of England (imputed data)

	Charlson				Ghali			
		EHR				EHR		
	% of		95% CI		% of		95% CI	
level	patients		lower	upper	patients		lower	upper
18 months to 6 months before diagnosis								
0	84.5	1.00	-	-	98.2	1.00	-	-
1	4.4	1.61	1.48	1.77	0.3	1.48	1.13	1.95
2	6.2	2.43	2.27	2.60	0.8	1.63	1.38	1.92
3+	4.9	3.65	3.39	3.94	0.7	2.16	1.86	2.51
6 months before diagnosis								
0	75.0	1.00	-	-	93.4	1.00	-	-
1	11.0	1.61	1.46	1.77	1.2	1.60	1.37	1.85
2	6.4	2.44	2.27	2.64	1.6	2.13	1.89	2.41
3+	7.6	3.66	3.38	3.97	3.2	2.82	2.59	3.06
First 12 months after diagnosis								
0	73.1	1.00	-	-	91.4	1.00	-	-
1	11.9	1.41	1.33	1.49	1.5	1.27	1.09	1.48
2	7.1	1.61	1.48	1.75	2.3	2.04	1.82	2.27
3+	7.9	2.21	1.92	2.54	4.8	2.31	2.14	2.50
Any time								
0	53.9	1.00	-	-	80.2	1.00	-	-
1	12.6	1.20	1.14	1.27	1.1	0.81	0.67	0.99
2	12.0	1.17	1.10	1.25	3.8	1.17	1.06	1.30
3+	21.5	1.46	1.38	1.53	14.9	1.64	1.56	1.73

Appendix 5.2: Relative distribution and excess hazard ratio of death for comorbidity measures of Charlson, Charlson with additions, Elixhauser and Ghali measure by time window (original 'complete' data): colorectal cancer patients diagnosed 1997-2004, North West of England

18 months to 6 months before diagnosis

	Charlson					modified Charlson					Elixhauser					Ghali				
	Patients		EHR	95% CI		Patients		EHR	95% CI		Patients		EHR	95% CI		Patients		EHR	95% CI	
level	No.	%		lower	upper	No.	%		lower	upper	No.	%		lower	upper	No.	%		lower	upper
0	28,244	95.5	1.00	-	-	28,110	95.1	1.00	-		27,759	93.9	1.00	-		29,014	98.1	1.00	-	
1	833	2.8	1.32	1.16	1.50	850	2.9	1.19	1.06	1.34	1,068	3.61	1.17	1.04	1.32	88	0.3	1.20	0.80	1.78
2	403	1.4	1.38	1.16	1.64	476	1.6	1.23	1.07	1.42	596	2.02	1.45	1.26	1.67	226	0.8	1.37	1.08	1.73
3+	85	0.3	2.85	2.12	3.83	127	0.4	1.78	1.45	2.17	140	0.47	1.53	1.15	2.03	237	0.8	2.06	1.70	2.51

6 months before to diagnosis

	Charlson					modified Charlson					Elixhauser					Ghali				
	Patients		EHR	95% CI		Patients		EHR	95% CI		Patients		EHR	95% CI		Patients		EHR	95% CI	
level	No.	%		lower	upper	No.	%		lower	upper	No.	%		lower	upper	No.	%		lower	upper
0	26,076	88.2	1.00	-		25,630	86.7	1.00	-		23,738	80.3	1.00	-		28,212	95.4	1.00	-	
1	2,552	8.6	1.52	1.41	1.63	2,651	9.0	1.27	1.18	1.35	3,930	13.3	1.27	1.19	1.35	279	0.9	1.26	1.10	1.68
2	705	2.4	2.32	2.08	2.60	970	3.3	1.56	1.43	1.71	1,551	5.3	1.59	1.45	1.74	355	1.2	2.18	1.85	2.55
3+	232	0.8	2.86	2.37	3.46	312	1.1	2.17	1.91	2.47	344	1.2	2.25	1.90	2.65	719	2.4	3.14	2.85	3.48

First 12 months after diagnosis

	Charlson					modified Charlson					Elixhauser					Ghali				
	Patients		EHR	95% CI		Patients		EHR	95% CI		Patients		EHR	95% CI		Patients		EHR	95% CI	
level	No.	%		lower	upper	No.	%		lower	upper	No.	%		lower	upper	No.	%		lower	upper
0	25,625	86.7	1.00	-		24,878	84.2	1.00	-		22,823	77.2	1.00	-		27,900	94.4	1.00	-	
1	2,742	9.3	1.21	1.12	1.30	3,044	10.3	0.85	0.78	0.90	4,483	15.2	0.89	0.84	0.96	328	1.1	0.94	0.75	1.18
2	912	3.1	1.32	1.17	1.49	1,233	4.2	1.06	0.97	1.16	1,793	6.1	1.07	0.98	1.18	448	1.5	1.98	1.72	2.28
3+	286	1.0	2.28	1.92	2.70	408	1.4	1.54	1.36	1.73	464	1.6	1.43	1.23	1.68	889	3.0	2.28	2.07	2.52

Any time

	Charlson					modified Charlson					Elixhauser					Ghali				
	Patients		EHR	95% CI		Patients		EHR	95% CI		Patients		EHR	95% CI		Patients		EHR	95% CI	
level	No.	%		lower	upper	No.	%		lower	upper	No.	%		lower	upper	No.	%		lower	upper
0	20,248	68.5	1.00	-	-	19,487	65.9	1.00	-	-	16,405	55.5	1.00	-	-	25,405	85.9	1.00	-	
1	3,313	11.2	0.96	0.89	1.03	3,420	11.6	0.75	0.69	0.80	4,833	16.4	0.82	0.77	0.88	295	1.0	0.37	0.25	0.54
2	2,813	9.5	0.83	0.77	0.91	2,833	9.6	0.76	0.70	0.82	3,658	12.4	0.70	0.65	0.76	844	2.9	0.86	0.74	1.00
3+	3,191	10.8	1.12	1.04	1.20	3,823	12.9	0.92	0.87	0.98	4,667	15.8	0.92	0.86	0.98	3,021	10.2	1.45	1.36	1.55

Appendix 5.3: Excess hazard ratio for death at five years and for Charlson and Ghali comorbidity measures at 18 to 6 months, adjusted for age, stage, deprivation and treatment (imputed data): colorectal cancer patients diagnosed 1997-2004, North West of England

		Charlson measure			Ghali measure		
		EHR			EHR		
			95% CI			95% CI	
level	Adjusted for		lower	upper		lower	upper
0		1.00	-	-	1.00	-	-
1	follow-up	1.61	1.48	1.77	1.48	1.13	1.95
2		2.43	2.27	2.60	1.63	1.38	1.92
3+		3.65	3.39	3.94	2.16	1.86	2.51
0	Age and follow-up	1.00	-	-	1.00	-	-
1		1.49	1.37	1.62	1.38	1.05	1.80
2		2.28	2.13	2.44	1.44	1.23	1.70
3+		3.17	2.94	3.41	1.74	1.50	2.02
0		1.00	-	-	1.00	-	-
1	Stage and follow-up	1.59	1.44	1.75	1.64	1.24	2.18
2		2.05	1.90	2.12	1.53	1.29	1.82
3+		2.82	2.59	3.07	2.26	1.93	2.64
0		1.00	-	-	1.00	-	-
1	Deprivation and follow-up	1.60	1.46	1.74	1.46	1.11	1.91
2		2.43	2.27	2.60	1.57	1.34	1.85
3+		3.61	3.35	3.89	2.10	1.81	2.44
0	Age, stage, deprivation, and follow-up	1.00	-	-	1.00	-	-
1		1.43	1.31	1.57	1.36	1.04	1.78
2		1.90	1.76	2.04	1.41	1.20	1.66
3+		2.38	2.19	2.60	1.71	1.47	1.98

Chapter 6

Do clinical and demographic variables explain socioeconomic inequalities in colorectal cancer survival?

Overview

Colorectal cancer survival decreases with increasing deprivation.[1-3] Some authors attribute these inequalities to deprived patients presenting with higher levels of comorbidity[4,5] or more advanced stage at diagnosis.[6,7] Comorbid conditions or advanced stage at diagnosis limit treatment options for treatment of curative intent. Very few patients with advanced colorectal cancer at diagnosis are amenable to curative treatment. Population-based evaluations of comorbidity and stage in cancer patients are difficult because data on stage and comorbidity are rarely complete in population-based data sources. Additionally, comorbidity and age are associated with other factors, such as treatment. Population-based assessments of the impact of stage, comorbidity and socioeconomic status on incidence and survival have usually been based on data in which stage and/or comorbidity are incomplete.[5,7,8] Alternatively, audits may have complete stage or comorbidity data but may not be representative of the general population.

Aim

Inequalities in colorectal cancer survival in the North West of England between 1997 and 2004 were evaluated to determine if they could be explained by stage, comorbidity and other clinical and demographic variables. The excess hazard ratio of death was estimated at one year after diagnosis, five years conditional on surviving the first year after diagnosis and at five years after diagnosis to determine if excess mortality occurred mainly during specific follow-up times thereby suggesting possible causal mechanisms. The excess hazard ratio of death in the most deprived compared to the most affluent (or 'deprivation gap') was evaluated for each clinical and demographic variable to determine the impact on the overall deprivation gap.

In order to assess inequalities in survival using complete data, particularly for stage, missing data were handled using multiple imputation. The impact of multiple imputation on associations and survival, particularly stage at diagnosis, was also

quantified. The analysis presented in this chapter will mainly be based on data after imputation, unless otherwise specified.

Imputation

Socioeconomic status was available for all patients, but many other variables which may explain inequalities were incomplete (e.g. stage, grade, histology and comorbidity, treatment). Multiple imputation methods were used to estimate missing data based on the observed dataset under the Missing at Random assumption. Multiple imputation did not substantially alter the distribution of stage, grade or histology compared to analysis of the original dataset for patients who were not missing data (or 'complete' analysis) but had a greater influence on the proportion of patients in each level of comorbidity, treatment regime, hospital and surgeon volume. Imputation did influence the stage-specific distribution for each variable, because deprived patients had higher levels of missing data. The similarity of distributions and excess mortality between the 'complete' and imputed analysis might supports the imputation methods. without obtaining the missing data it is not possible to determine (or test) if the assumption that unobserved data is missing at random (MAR).[9]

The proportion of patients with missing grade increased from 22.4% of affluent patients to 26.7% of deprived patients with a corresponding decrease in the proportion of grade II and III cancers in deprived patients (Table 6.1). Similarly, the proportion of patients with unspecified histology increased with deprivation. After imputation there was no significant variation in grade or histological type by socioeconomic status. Grade IV and other histological types were very rare and imputation had very little effect on the distribution of these. The higher proportion of incomplete grade and histology in deprived patients was associated with a slightly lower proportion of colorectal cancers diagnosed in deprived patients being confirmed by pathologically. Colorectal cancer was confirmed by pathology (tissue diagnosis) in 92.6% of deprived patients compared to 94.3% of affluent patients with the remainder diagnosed by imaging (affluent 2.0%, deprived 2.9%) or clinically (without imaging or tissue diagnosis) (affluent 3.6%, deprived 4.4%).

Affluent patients were more likely to have missing comorbidity data (21.1%, n=1,022) but after imputation, affluent patients were more likely to have no comorbidity (88.2%) than deprived patients (85.2%) (Table 6.1). Higher levels of comorbidity in deprived patients were associated with an increased risk of hospital admissions and a slightly lower level of missing comorbidity measures than affluent. After imputation patients

with comorbidity level two were more prevalent than level one or three, but the excess hazard ratio of death increased consistently with each level of comorbidity (Table 6.1, Table 6.4). The higher proportion of patients with a comorbidity in level two, compared to comorbidity levels of one or three or more is probably because of the close relationship between diseases with a weight of two and poor survival. Patients with a comorbidity level of two either had two low level comorbid conditions (each with weight of one) or, as is more likely to occur, had diseases with a weight of two (paraplegia, renal disease or diabetes with complications). Paraplegia and renal disease were both individually associated with a significant excess mortality (see Table 5.4), therefore resulting in comorbidity level two having an excess hazard ratio of death for each comorbidity level intermediate between level one and level three or more. Comorbidity was more strongly associated with increasing deprivation after imputation (Table 6.1), because there was a higher proportion of missing comorbidity data for affluent patients (after imputation: no comorbidity in 88.2% of affluent and 85.2% of deprived). The odds ratio of having any comorbidity, compared to none, increased with deprivation and was significant, even after adjustment for clinical and demographic factors (see Table 5.5).

Table 6.1: Distribution (%) of clinical and treatment factors by deprivation among observed 'complete' data and after imputation colorectal cancer patients diagnosed 1997-2004, North West of England

	Original "complete" data						Imputed					
	1 - affluent	2	3	4	5 - deprived	all	1 - affluent	2	3	4	5 - deprived	all
Clinical factors												
Stage												
I	13.2	12.8	12.0	11.5	11.4	**12.3**	11.7	11.9	10.9	10.2	10.2	**10.8**
II	38.6	40.2	41.0	42.2	42.0	**41.0**	36.8	37.6	38.4	38.7	38.3	**38.0**
III	44.2	43.0	42.8	43.3	42.8	**43.2**	46.6	46.1	45.8	46.9	46.7	**46.8**
IV	4.0	3.1	4.2	3.0	3.7	**3.6**	4.9	4.3	4.9	4.3	4.8	**4.8**
Not known	(37.2)	(38.4)	(39.1)	(40.3)	(41.2)	**(39.5)**						
Grade												
I	13.2	15.2	14.7	14.5	14.7	**14.5**	12.9	14.2	14.0	13.9	13.9	**13.8**
II	73.1	71.8	72.1	72.1	72.7	**72.4**	72.5	71.7	71.8	72.0	72.5	**72.1**
III	13.3	12.8	12.9	13.0	12.4	**12.8**	14.2	13.8	13.9	13.8	13.3	**13.7**
IV	0.4	0.2	0.3	0.3	0.2	**0.3**	0.4	0.3	0.3	0.3	0.3	**0.3**
Not known	(22.4)	(24.4)	(25.1)	(25.3)	(26.7)	**(25.0)**						
Histology												
Adenocarcinoma	90.8	90.8	91.3	90.0	90.6	**80.1**	90.7	90.7	91.2	90.1	90.5	**90.6**
Mucinous and serous	8.9	8.7	8.2	9.6	8.8	**7.8**	8.9	8.7	8.3	9.5	8.9	**8.9**
Other specified	0.3	0.5	0.5	0.4	0.6	**0.4**	0.4	0.5	0.5	0.4	0.6	**0.5**
Neoplasm NOS	(8.8)	(10.3)	(12.1)	(12.7)	(12.9)	**(11.6)**						
Comorbidity												
none	95.7	95.4	94.8	94.1	93.5	**94.5**	88.2	87.7	86.6	86.2	85.2	**86.5**
1	2.7	3.0	3.1	4.1	3.9	**3.5**	3.5	3.6	3.7	4.5	4.3	**4.0**
2	1.4	1.4	1.9	1.4	2.1	**1.7**	5.2	5.2	5.8	5.1	5.8	**5.5**
3+	0.2	0.3	0.2	0.4	0.6	**0.4**	3.1	3.5	3.9	4.2	4.7	**4.0**
Unknown	(21.0)	(18.8)	(18.6)	(18.0)	(19.8)	**(19.3)**						
Treatment factors												
Treatment												
surgery only	62.2	62.7	64.8	63.5	65.1	**63.8**	36.6	36.7	39.6	40.2	41.3	**39.2**
surgery and chemo	14.2	14.0	10.8	12.0	11.0	**12.2**	37.2	37.8	34.6	33.9	33.2	**35.1**
surgery and radiotherapy	7.5	7.1	7,64	7.7	6.9	**7.3**	1.0	0.8	0.7	0.9	0.8	**0.8**
surgery and chemoradio	4.4	4.4	3.9	4.5	4.2	**4.3**	16.0	15.5	15.5	15.6	14.7	**15.3**
chemotherapy only	2.0	2.0	2.0	1.8	1.7	**1.9**	0.5	0.4	0.3	0.3	0.4	**0.4**
radiotherapy only	0.9	0.6	0.6	0.7	0.5	**0.7**	0.5	0.3	0.3	0.3	0.2	**0.3**
chemoradiotherapy	1.1	0.9	1.2	1.1	1.1	**1.1**	0.7	0.4	0.3	0.4	0.2	**0.4**
no treatment	7.7	8.3	9.0	8.7	9.6	**8.8**	7.5	8.1	8.8	8.4	9.3	**8.5**
missing	(4.5)	(5.8)	(6.3)	(7.2)	(7.7)	**(6.5)**						
Hospital volume												
very high (over 150)	22.2	25.3	23.2	20.6	22.2	**22.6**	24.8	27.9	26.3	25.1	26.6	**26.2**
high (100 to 149)	27.5	30.2	33.4	31.0	31.3	**30.8**	31.4	34.1	37.5	36.2	36.7	**35.4**
moderate (50 to 99)	21.1	16.4	16.5	17.8	15.0	**17.1**	23.0	18.6	19.0	20.7	17.9	**19.6**
low (less than 50)	4.6	5.3	4.1	5.5	6.1	**5.2**	5.3	5.9	4.8	6.2	6.8	**5.9**
Private	5.9	3.3	1.7	0.9	0.4	**2.1**	5.8	3.5	2.0	1.3	0.9	**2.4**
none	18.9	19.6	21.2	24.3	25.1	**22.2**	9.7	10.1	10.5	10.5	11.2	**10.5**
missing	(24.2)	(25.7)	(27.9)	(31.2)	(32.3)	**(28.9)**						
Surgeon volume												
very high (over 60)	4.6	2.7	2.1	2.3	1.6	**2.5**	5.0	3.1	2.5	2.7	1.9	**2.9**
high (40 to 59)	13.4	14.0	13.0	13.0	14.6	**13.7**	12.9	16.3	14.9	15.0	16.0	**15.7**
moderate (20 to 39)	27.5	28.2	29.2	28.9	27.2	**28.1**	33.3	33.3	33.8	33.2	31.2	**32.7**
low (less than 20)	28.6	30.5	31.6	32.0	24.0	**31.7**	35.3	37.1	38.1	38.7	39.8	**38.2**
none	25.8	24.6	24.2	23.8	22.5	**24.0**	10.0	10.2	10.8	10.5	11.1	**10.6**
missing	(15.7)	(16.9)	(18.4)	(18.6)	(19.6)	**(18.1)**						
	100.0	100.0	100.0	100.0	100.0	**100.0**	100.0	100.0	100.0	100.0	100.0	**100.0**

After imputation patients with missing stage were more likely to have an advanced stage than patients with known stage at diagnosis (Table 6.1 and 6.2). After imputation there were a much higher proportion of patients with missing stage diagnosed in stage III (53%) and stage IV (6.3%) compared to the overall distribution of stage. The most common stage at diagnosis before imputation was stage II and III (41%, 43%) but after

imputation for all patients this shifted towards more advanced disease (stage II 38%, stage III 46%). Obviously, unstaged patients were predominantly patients who were not treated surgically and where therefore associated with missing grade and histology; 10.3% (n=3,059) of patients were missing all three (stage, grade and histology). Increasing deprivation was associated with a higher proportion of patients with missing stage (Table 6.1), although this was explained by variations in age, sex, subsite, year of diagnosis and treatment (see Table 3.14). The proportion of patients in each stage at diagnosis was similar across all socioeconomic groups both before and after imputation. Stage I was slightly more common in more affluent patients whereas stage II was slightly less common possibly reflecting the impact of private health checks and opportunistic screening.

Table 6.2: Distribution (%) of stage for patients with known (observed 'complete' data) stage, imputed stage and for patients with missing but imputed stage: colorectal cancer patients diagnosed 1997-2004, North West of England

Stage	complete stage		Imputed†	
			missing stage (n=11,684)	All
	No.	%	%	%
I	2,191	12.3	8.7	10.8
II	7,322	41.0	33.5	38.0
III	7,722	43.2	51.5	46.8
IV	644	3.6	6.3	4.8
unknown	11,684	(39.4)	-	-
		100.0	100.0	100.0

† Analysis of 10 imputed datasets

Imputation is expected to produce distributions that are more representative of the 'true' underlying data and provide more plausible (and interpretable) estimates than the incomplete (original) data.

Patients with missing stage had poorer survival than staged patients but were estimated to be from a heterogeneous mix of 'true' stages, with a higher proportion of advanced disease than patients with known stage. Therefore, before imputation patients with missing stage had a relative survival at five years in between (32.4%) that of stage III (42.8%) and IV (10.5%) (Figure 6.1). After imputation one-year and five-year relative survival for each stage was lower than before imputation (Table 6.3). The poorer prognosis for patients with missing stage resulted in large decreases in survival compared to 'complete' survival analysis for stage III and IV, particularly at one-year.

Figure 6.1: Relative survival (%) up to five years after diagnosis for unimputed and imputed data by stage at diagnosis: colorectal cancer patients diagnosed 1997-2004, North West of England

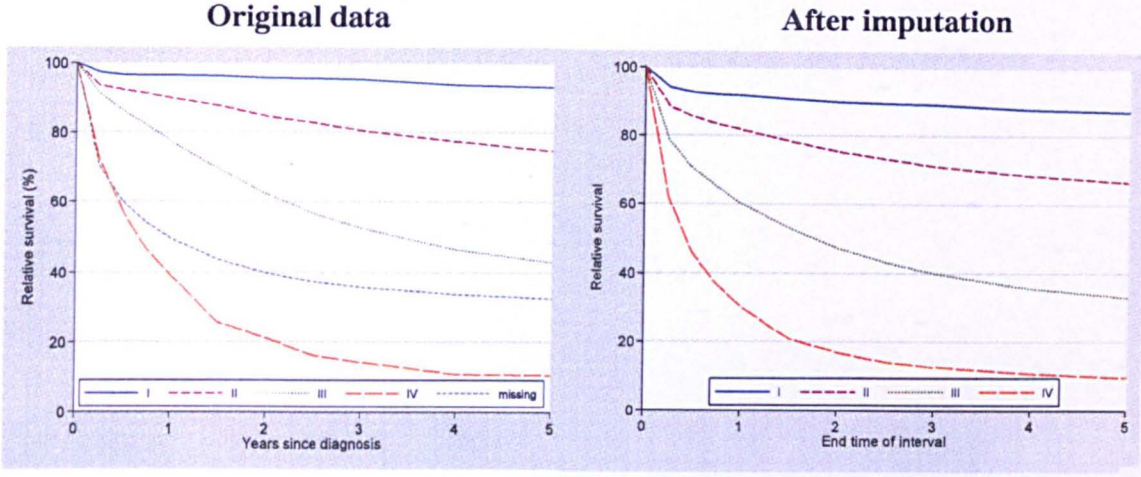


Table 6.3: Relative survival (%) up to five years after diagnosis for original data and data after imputation by stage at diagnosis: colorectal cancer patients diagnosed 1997-2004

	unimputed		imputed	
Stage	one-year	five-year	one-year	five-year
I	96.5	93.3	90.1	87.2
II	89.8	74.7	78.3	66.5
III	77.3	42.8	52.8	32.8
IV	39.2	10.5	20.8	9.4
missing	49.5	32.4		

The three approaches used to handle missing data included i) limiting analysis to patients with complete data ('complete' analysis), ii) analysis with a separate category for missing data (or 'interval' analysis) and iii) using the imputed 'complete' dataset created by multiple imputation. All three approaches produced relatively similar excess hazard ratios of death (or 'excess mortality') for each level of grade, comorbidity and histology. Wider differences occurred for each level of stage (Table 6.4).

Stage

In the complete analysis, the excess hazard ratio of death for stage increased rapidly to 3.89 in stage II, 11.65 in stage III and 30.13 in stage IV, compared with stage I (reference category) (Table 6.4). The excess hazard ratio for stages I to IV increased consistently and moderately for the interval analysis compared to the complete analysis. Patients with missing stage in the interval analysis had an excess hazard ratio of 12.64 (95% CI 9.47, 16.86) intermediate between stage III and IV. After imputation, the excess hazard ratio of death in relation to stage increased less rapidly with stage than either complete or interval analysis.

Grade

Complete and interval analysis had similar excess hazard ratios for grades I to IV. The excess hazard ratio for patient with missing grade was between grade III and IV (Table 6.4). In the imputed analysis the excess hazard for grade IV was higher but otherwise imputed analysis was broadly similar to the complete and interval analysis.

Histology

Patients with adenocarcinoma consistently had the best survival regardless of the approach to handling missing data. The excess hazards of death for adenocarcinoma and mucinous and serous histological types were similar in complete, interval and imputed analysis (Table 6.4). It was difficult to interpret analyses of the other specified histological type because there was a very small proportion of patients (complete analysis: n=128) which resulted in wide variations between complete, interval and imputed analysis. It is unsurprising that survival was very low for patients with an unspecified histology (Neoplasm, not otherwise specified) because they were unlikely to undergo surgery and, therefore unlikely to have pathological confirmation of their colorectal cancer (as described previously for missing stage).

Comorbidity

Interval and complete analysis produced similar estimates of the excess hazard ratio of death for each comorbidity level (none to 3 or more) whereas after imputation the excess hazard for each comorbidity level was higher (Table 6.4). Patients with missing comorbidity had higher survival (0.85 95% CI 0.74, 0.96) than those without comorbidity possibly indicating a 'true' lack of comorbidity in these patients. After imputation a high proportion of patients with missing comorbidity were imputed to have

no comorbidity, thereby improving the survival in the no comorbidity group (reference category) and systematically increasing the excess hazard ratio in levels one to three or more.

Table 6.4: Excess hazard ratio (EHR) of death at five years after diagnosis for records no missing data (original 'complete' analysis), with a separate 'missing' category (interval analysis) and with data after imputation adjusted for follow-up and age: colorectal cancer patients diagnosed 1997-2004, North West of England

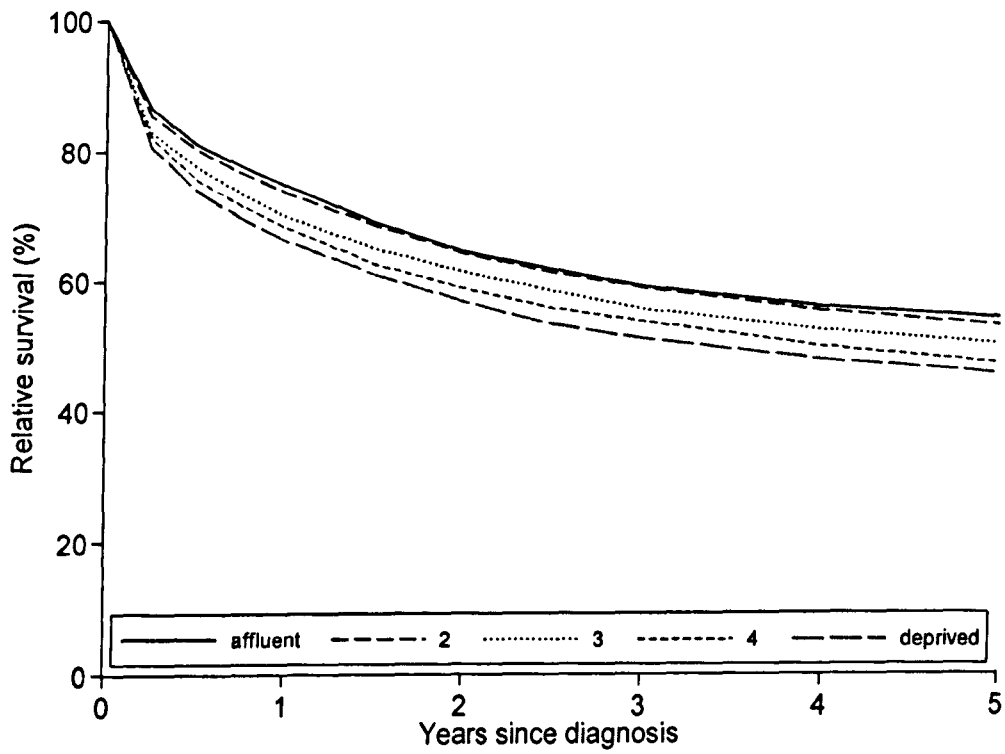
	Complete (16,223)			Interval (n=29,563)			Imputed (n=29,563)		
	EHR	95% CI		EHR	95% CI		EHR	95% CI	
		lower	upper		lower	upper		lower	upper
Clinical factors									
Stage									
I	1.00	-	-	1.00	-	-	1.00	-	-
II	3.89	2.81	5.40	3.66	2.73	4.90	2.69	2.32	3.11
III	11.65	8.44	16.08	9.76	7.31	13.04	6.87	6.05	8.02
IV	30.13	21.42	42.38	21.69	16.07	29.28	15.30	12.12	17.85
missing	-	-	-	12.64	9.47	16.86	-	-	-
Grade									
I	1.00	-	-	1.00	-	-	1.00	-	-
II	1.38	1.24	1.55	1.34	1.20	1.49	1.46	1.37	1.57
III	3.29	2.90	3.73	3.08	2.74	3.47	3.00	2.77	3.24
IV	3.38	1.66	6.87	3.43	2.19	5.37	3.68	2.82	4.81
missing	-	-	-	2.61	2.33	2.93	-	-	-
Comorbidity									
0	1.00	-	-	1.00	-	-	1.00	-	-
1	1.54	1.31	1.80	1.50	1.31	1.71	1.62	1.48	1.77
2	1.55	1.21	1.98	1.51	1.24	1.85	2.43	2.27	2.60
3+	2.84	1.76	4.58	2.94	2.12	4.08	3.65	3.39	3.94
missing	-	-	-	0.85	0.74	0.96	-	-	-
Histology									
Adenocarcinoma	1.00	-	-	1.00	-	-	1.00	-	-
Mucinous and serous	1.29	1.16	1.42	1.22	1.14	1.31	1.20	1.12	1.27
Other specified	2.74	1.50	5.01	1.07	0.85	1.35	1.78	1.44	2.21
Neoplasm NOS	-	-	-	2.29	2.15	2.43	-	-	-
Treatment factors									
Hospital volume									
very high (over 150)	1.00	-	-	1.00	-	-	1.00	-	-
high (100 to 149)	0.98	0.92	1.04	0.98	0.92	1.04	0.97	0.92	1.02
moderate (50 to 99)	1.00	0.93	1.07	1.00	0.93	1.07	0.97	0.91	1.03
low (less than 50)	1.21	1.10	1.33	1.21	1.10	1.33	1.11	1.02	1.21
private	0.47	0.38	0.57	0.47	0.38	0.57	0.55	0.46	0.65
none	1.88	1.78	1.99	1.88	1.77	1.99	2.86	2.70	3.03
missing	-	-	-	3.41	3.20	3.63	-	-	-
Consultant volume									
very high (60 and over)	1.00	-	-	1.00	-	-	1.00	-	-
high (40 to 59)	1.02	0.87	1.20	1.02	0.87	1.21	1.03	0.89	1.19
moderate (20 to 39)	1.06	0.90	1.23	1.08	0.92	1.27	1.11	0.97	1.27
low (less than 20)	1.53	1.31	1.78	1.55	1.33	1.81	1.57	1.37	1.79
none	2.43	2.08	2.83	2.51	2.15	2.93	3.81	3.32	4.37
missing	-	-	-	5.26	4.49	6.16	-	-	-
Treatment									
surgery only	1.00	-	-	1.00	-	-	1.00	-	-
surgery and chemotherapy	1.27	1.20	1.35	1.27	1.20	1.35	0.95	0.90	1.00
surgery and radiotherapy	0.87	0.79	0.95	0.87	0.79	0.95	0.69	0.51	0.92
surgery and chemoradiotherapy	1.33	1.22	1.45	1.33	1.22	1.45	0.91	0.85	0.97
radiotherapy only	2.69	2.40	3.01	2.69	2.40	3.01	1.12	0.82	1.56
chemotherapy only	1.79	1.47	2.18	1.79	1.47	2.18	1.20	0.82	1.75
chemoradiotherapy	2.21	1.89	2.59	2.21	1.89	2.59	1.09	0.81	1.46
no treatment	8.98	8.48	9.51	8.98	8.48	9.51	3.37	3.17	3.59
missing	-	-	-	5.27	4.98	5.57	-	-	-

Analyses of treatment factors were included in tables for reference but the results will be described in Chapter 7. Unless otherwise specified all subsequent analysis will be based on the imputed dataset.

Socioeconomic status

Higher levels of deprivation were associated with poorer survival at all follow-up times (3 months to 5 years) (Figure 6.2). The inequality in survival between deprived and affluent, also known as the 'deprivation gap', was established and significant by one year after diagnosis with the magnitude of the deprivation gap stable at two, three, four and five years after diagnosis (7.3%-7.9%). The consistently lower survival in deprived patients culminated in some startlingly wide inequalities. For example deprived patients have a median survival 40% shorter than affluent patients (deprived: 2.10 yrs 95% CI 2.10, 2.21, affluent: 3.49 yrs 95% CI 3.21, 3.89). Some of the deprivation gap may be explained by other factors, particularly those influencing prognosis (e.g. stage) or appropriateness of treatment (e.g. age, comorbidity), however if a deprivation gap occurs for each variable (e.g. stage, comorbidity) the deprivation gap will not be moderated after adjustment for these factors.

Figure 6.2: Relative survival (%) up to five years after diagnosis by deprivation group: colorectal cancer patients diagnosed 1997-2004, North West of England



Inequalities in survival were estimated using the excess hazard ratio of death for the deprived compared to the affluent (reference category) at one year after diagnosis and conditional at five years after diagnosis (conditional on surviving the first year) (Table 6.5 and 6.6). These time periods were chosen because i) stage and comorbidity strongly influence the first year after diagnosis, ii) treatment has a greater effect on survival after

the first year of diagnosis and iii) the deprivation gap was established in the first year after diagnosis. The excess hazard ratio of death was estimated for each socioeconomic group and assuming a linear deprivation gap. In order to easily compare the excess hazard ratio in the most deprived to the linear deprivation gap the linear coefficient of the continuous deprivation gap was multiplied by the four gaps between each deprivation groups. The linear deprivation gap and the excess hazard for the most deprived were similar for most analysis, therefore unless otherwise stated the linear deprivation gap will be discussed.

Significant deprivation gaps (based on the linear estimate) occurred for 20 of 24 categories at one year but only 11 of the 24 categories following the first year of diagnosis (or 'conditional' survival). At one year after diagnosis the deprivation gap was substantial (EHR 1.33) but narrowed to an excess hazard of death of 1.18 for five year conditional survival (Table 6.6).

The deprivation gap narrowed at for one-year and conditional survival for factors associated with a poor prognosis, although the trend was more pronounced in the first year. For example increasing age was associated with a narrowing of the deprivation gap in the first year from an excess hazard of death of 1.73 for patients aged 45 to 54 to 1.16 for patients aged 85 to 99 (Table 6.5). There was also a narrowing of the deprivation gap with increasing age for five-year conditional survival but it was less pronounced than in the first year (1.32 in patients aged 45 to 55 to 1.00 in patients aged 85 to 99). Similarly, increasing levels of stage, grade and increasing specificity of histology were associated with a narrowing of the deprivation gap for one year and conditional survival.

Table 6.5: Excess hazard ratio of death at one year after diagnosis by deprivation group for clinical and demographic variables, adjusted for age and follow-up (reference = affluent) (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

	1 - affluent	2	3	4	5 - deprived	Linear coefficient of deprivation gap†	
All	1.00	1.03	1.15	1.23	1.35	1.33	*
Gender							
Men	1.00	0.96	1.17	1.23	1.35	1.36	*
Women	1.00	1.11	1.14	1.22	1.35	1.29	*
Age group							
15 to 44	1.00	0.68	0.62	0.97	1.17	1.08	
45 to 54	1.00	1.05	1.56	1.89	1.85	1.73	*
55 to 64	1.00	1.08	1.27	1.39	1.74	1.61	*
65 to 74	1.00	1.00	1.11	1.22	1.42	1.41	*
75 to 84	1.00	1.00	1.07	1.12	1.17	1.18	*
85 to 99	1.00	1.11	1.25	1.22	1.21	1.16	*
Subsite (ICD-10)							
Colon (C18)	1.00	1.04	1.15	1.27	1.36	1.34	*
Rectosigmoid (C19)	1.00	0.95	0.88	1.13	1.31	1.35	*
Rectum (C20)	1.00	1.00	1.25	1.16	1.35	1.32	*
Stage							
I	1.00	1.09	1.19	1.11	1.39	1.48	
II	1.00	1.02	1.18	1.31	1.42	1.40	*
III	1.00	1.04	1.15	1.23	1.35	1.32	*
IV	1.00	1.13	1.22	1.23	1.29	1.23	
Grade							
I	1.00	0.81	1.10	1.21	1.27	1.37	*
II	1.00	1.06	1.19	1.27	1.43	1.38	*
III	1.00	1.08	1.11	1.20	1.27	1.24	*
IV	1.00	0.94	1.27	0.84	1.48	1.32	*
Histology							
Adenocarcinoma	1.00	1.02	1.15	1.21	1.34	1.32	*
Mucinous and serous	1.00	1.00	1.22	1.44	1.39	1.40	*
Other specified	1.00	1.63	1.15	0.79	1.14	0.82	
Comorbidity							
0	1.00	1.00	1.13	1.23	1.33	1.33	*
1	1.00	0.99	1.24	1.03	1.11	1.09	
2	1.00	1.14	1.18	1.27	1.33	1.27	*
3+	1.00	1.25	1.28	1.25	1.38	1.25	

* p-value<0.05

† Regression for linear change in EHR between successive socioeconomic groups (estimated by multiplying the linear coefficient by 4 to obtain entire deprivation gap),

Table 6.6: Excess hazard ratio of death at five years conditional on surviving the first year after diagnosis, by deprivation group, for clinical and demographic variables, adjusted for age and follow-up (reference = affluent) (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

	1 - affluent	2	3	4	5 - deprived	Linear coefficient of deprivation gap†	
All	1.00	1.00	1.04	1.13	1.17	1.18	*
Gender							
Men	1.00	1.08	1.12	1.16	1.26	1.22	*
Women	1.00	0.90	0.95	1.10	1.05	1.09	
Age group							
15 to 44	1.00	0.75	0.55	1.23	1.40	1.32	*
45 to 54	1.00	0.88	0.81	1.23	1.00	1.12	
55 to 64	1.00	0.93	0.91	0.96	1.23	1.22	*
65 to 74	1.00	1.23	1.37	1.20	1.32	1.21	*
75 to 84	1.00	0.96	1.04	1.06	1.04	1.06	
85 to 99	1.00	0.76	0.89	1.02	0.87	1.00	
Subsite (ICD-10)							
Colon (C18)	1.00	1.04	0.96	1.08	1.11	1.10	
Rectosigmoid (C19)	1.00	0.89	1.11	1.18	1.42	1.44	*
Rectum (C20)	1.00	0.97	1.19	1.22	1.21	1.24	*
Stage							
I‡	1.00	1.34	1.91	1.91	2.37	1.76	
II	1.00	1.11	1.16	1.24	1.35	1.29	*
III	1.00	1.00	1.00	1.12	1.12	1.16	*
IV‡	1.00	1.08	1.01	1.07	1.27	1.27	
Grade							
I	1.00	1.03	0.99	1.09	1.11	1.11	
II	1.00	1.01	1.05	1.15	1.22	1.22	*
III	1.00	1.08	1.23	1.36	1.15	1.21	
IV‡	1.00	-	-	-	-	-	
Histology							
Adenocarcinoma	1.00	1.02	1.07	1.18	1.21	1.21	*
Mucinous and serous	1.00	2.67	1.65	1.48	1.46	1.11	
Other specified	-	-	-	-	-	1.01	
Comorbidity							
0	1.00	1.01	1.04	1.15	1.17	1.19	*
1	1.00	0.92	0.95	1.00	1.29	1.31	
2	1.00	1.19	1.19	1.09	1.21	1.12	
3+	1.00	1.02	1.62	1.59	1.44	1.42	

* p-value<0.05

† Regression for linear change in EHR between successive socioeconomic groups (estimated by multiplying the linear coefficient by 4 to obtain entire deprivation gap),

‡ Not adjusted for age due to low numbers of deaths,

Demographic factors

Sex

Overall survival at one year and conditional survival at five years was slightly lower in women than men even after adjustment for clinical and demographic factors (Table 6.7). The average life expectancy for women in the general population is higher than men however the use of relative survival and adjustment for age and other factors (stage,

comorbidity, etc.) accounts for these differences. Some authors have suggested that women may have better biological responses to trauma[10,11] and therefore better survival after surgery, although the main impact of this would be expected post-operatively and in the first year after diagnosis. Higher survival and lack of inequalities in survival in women than men after the first year of diagnosis is more likely to be because of gender differences in colorectal cancer subsite. Men are more likely to have rectal (and rectosigmoidal) cancer than women (colon: men 57%, women 67%; rectosigmoidal: men 9%, women 7%, rectal: men 34%, women 26%).

In the first year after diagnosis socioeconomic inequalities in survival were similar for both men and women (EHR 1.36 in men and 1.29 in women). For women there was no socioeconomic trend for five year conditional survival, in particular women from group 2 and 3 had better survival than affluent women. For men there was still a deprivation gap in conditional survival at five years, although it was narrower than the deprivation gap at one year.

Table 6.7: Excess hazard ratio of death at one year after diagnosis and five year survival conditional on surviving the first year after diagnosis, for clinical and demographic variables (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

	One year			Five year survival conditional on surviving the first yeat		
		95% CI			95% CI	
Deprivation group						
1 - affluent	1.00	-	-	1.00	-	-
2	1.03	0.94	1.14	1.03	0.92	1.15
3	1.14	1.04	1.26	1.03	0.92	1.15
4	1.22	1.11	1.34	1.14	1.02	1.27
5 - deprived	1.34	1.23	1.46	1.16	1.05	1.29
Comorbidity						
0	1.00	-	-	1.00	-	-
1	1.54	1.39	1.70	1.52	1.30	1.77
2	1.72	1.54	1.92	1.63	1.36	1.94
3+	2.02	1.66	2.47	1.89	1.32	2.71
Gender						
Men	1.00	-	-	1.00	-	-
Women	0.97	0.92	1.03	0.91	0.85	0.97
Age group						
15 to 44	1.00	-	-	1.00	-	-
45 to 54	1.22	0.95	1.58	1.17	0.96	1.44
55 to 64	1.64	1.30	2.07	1.16	0.96	1.41
65 to 74	2.20	1.76	2.76	1.23	1.02	1.49
75 to 84	3.25	2.59	4.07	1.27	1.05	1.55
85 to 99	4.88	3.87	6.15	1.52	1.18	1.94
Subsite (ICD-10)						
Colon (C18)	1.00	-	-	1.00	-	-
Rectosigmoid (C19)	0.83	0.75	0.92	1.06	0.94	1.20
Rectum (C20)	0.77	0.73	0.82	1.14	1.06	1.23
Stage						
I	1.00	-	-	1.00	-	-
II	2.11	1.75	2.54	4.04	2.93	5.57
III	4.84	4.04	5.80	11.70	8.53	16.04
IV	9.96	8.17	12.14	24.83	17.65	34.93
Histological type						
Adenocarcinoma	1.00	-	-	1.00	-	-
Mucinous and serous	0.93	0.85	1.02	1.20	1.08	1.34
Other specified	1.17	0.89	1.53	0.76	0.45	1.28
Grade						
I	1.00	-	-	1.00	-	-
II	1.05	0.95	1.15	1.14	1.03	1.27
III	2.07	1.87	2.31	1.43	1.25	1.64
IV	2.55	1.86	3.49	1.34	0.71	2.53

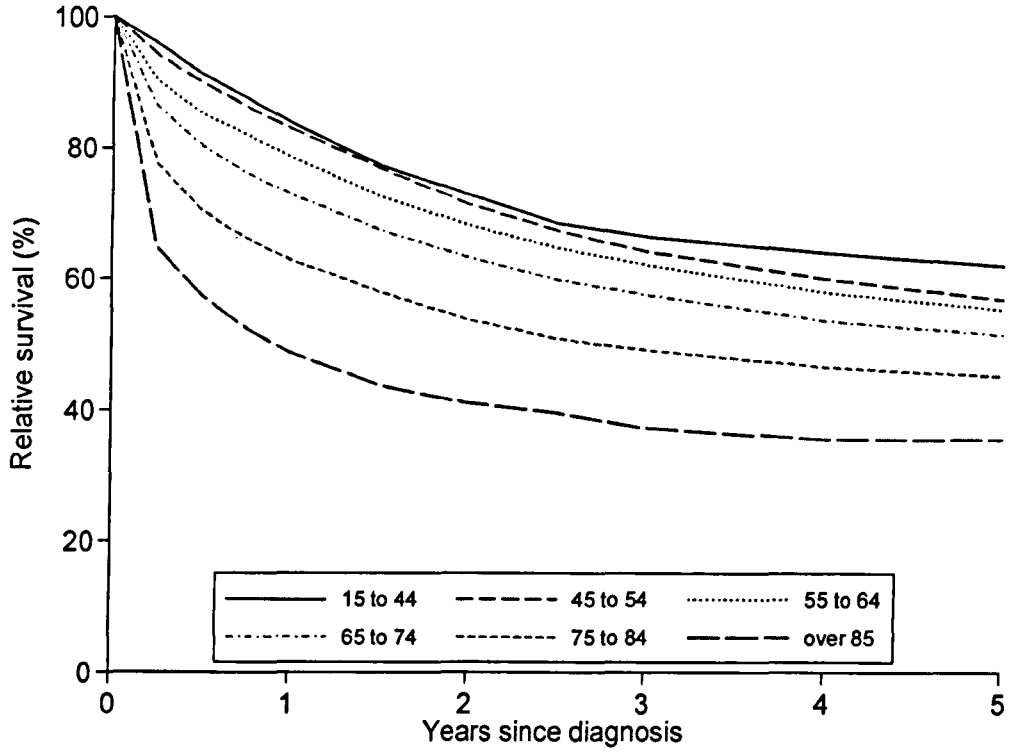
* Adjusted for all variables in the table

Age at diagnosis

Survival decreased with increasing age, with a rapid decline (or high excess mortality) occurring within the first 3 months after diagnosis for patients aged over 75 (Figure 6.3). There were substantial age-specific differences in relative survival at five years after diagnosis ranging from 62.3% (95% CI 58.4, 66.0) for patients aged 15 to 44 to 35.6% (95% 32.1-39.2) for patients aged 85 to 99 at diagnosis. Wide variations in age-specific survival at five years after diagnosis were mainly explained by age-specific differences in the first year after diagnosis with very little difference in age-specific five year conditional survival (Table 6.7). For example at one year after diagnosis patients aged 85 to 99 had an adjusted excess hazard ratio of death of 4.88, compared to patients age 15 to 44, while for conditional survival at five years the excess hazard of death was only 1.52 for patients age 85 to 99.

Inequalities in survival decreased with increasing age for both one year survival and conditional survival at five years, however the inequalities were wider at one year than for five year conditional survival (Table 6.5 and 6.6). Patients aged over 75 had a small deprivation gap at one year but this disappeared after the first year. For patients over 75 higher levels of comorbidity and lower survival are stronger influences and may cancel out any inequalities in survival. The only age to see an increase in the deprivation gap between one year survival and conditional five year survival was patients age 15 to 44 although they had a very high overall survival. A higher proportion of younger patients may have colorectal cancer with a genetic aetiology, therefore they may be diagnosed earlier through familial screening or have preventative treatment decreasing the likelihood of mortality and the deprivation gap within the first year after diagnosis.

Figure 6.3: Relative survival (%) up to five years after diagnosis by age group: colorectal cancer patients diagnosed 1997-2004, North West of England



Clinical factors

Stage

Advancing stage was very strongly associated with poorer survival. After the first year of diagnosis the excess hazard of death was more strongly associated with stage than at one year after diagnosis (Table 6.7). This may be because in the first year after diagnosis post-operative mortality contributes substantially to excess mortality. Post-operative mortality was associated with all stages, although most frequently in patients with comorbidity. Colorectal cancer in patients with advanced stage generally causes death after the first year. Trends in treatment and survival will be further discussed in chapter 8.

A narrowing of the deprivation gap was associated with advancing stage at diagnosis at one year and five year conditional survival (Table 6.5 and 6.6). The socioeconomic inequality in survival narrowed for moderate stage tumours (stage II and III) conditional on surviving the first year after diagnosis, but remained significant. For example, the linear deprivation gap (or excess hazard of death) for stage III was 1.32 at one year after diagnosis, but decreased to 1.16 for five year survival conditional on surviving the first year after diagnosis. It may be unsurprising that inequalities are significant for moderate

stage because the inter-relationship of other factors (e.g. comorbidity) and treatment choices may have the biggest impact on survival for these stages. Whereas, there is less ambiguity or influence of other factors (e.g. comorbidity) in the treatment regimes for early and advanced stage tumours. For stage I and IV the excess hazard of death could not be adjusted for age because of the small number of patients by age group and for stage I the low number of deaths.

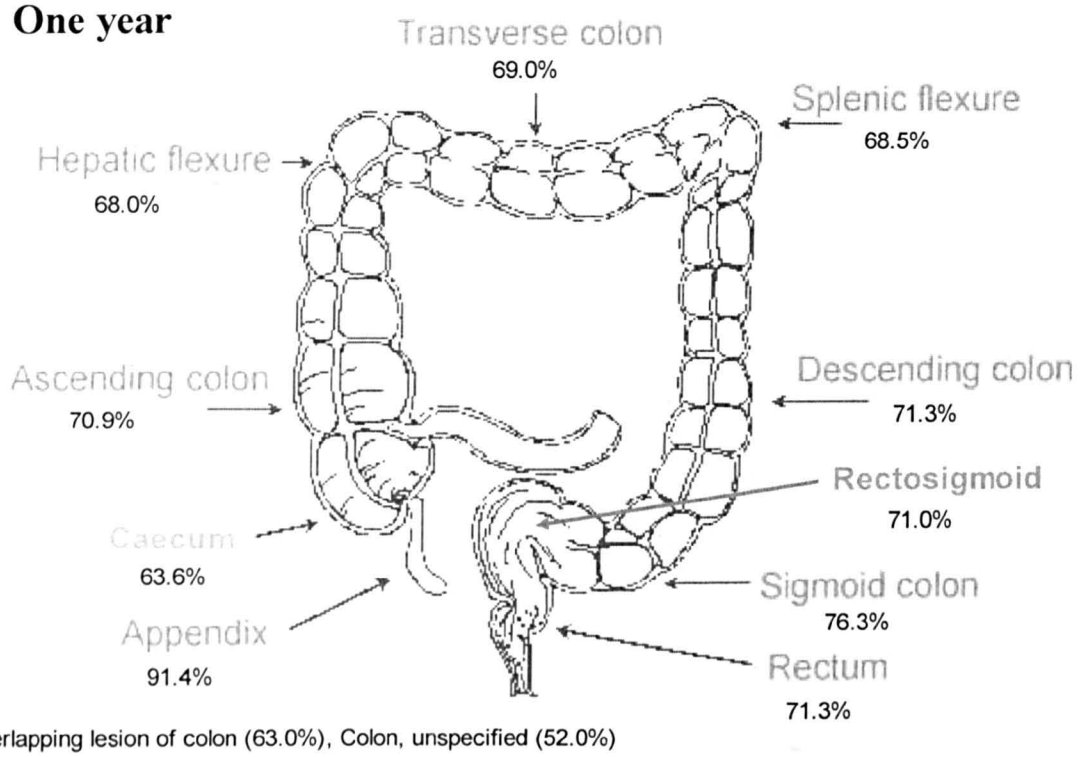
Specific site

Variations in survival by specific cancer site were evaluated to determine if specific site could elucidate further socioeconomic variations in survival. Specific cancer site was only available for colon cancer, with a large proportion of colon cancer patients having unspecified (n=4,099, 13.9%) or overlapping sites (n=303, 1.0%). Cancers of the caecum, colon unspecified, and overlapping lesion had the lowest relative survival at both one and five years and were associated with non-surgical treatment and older age (Figure 6.4).

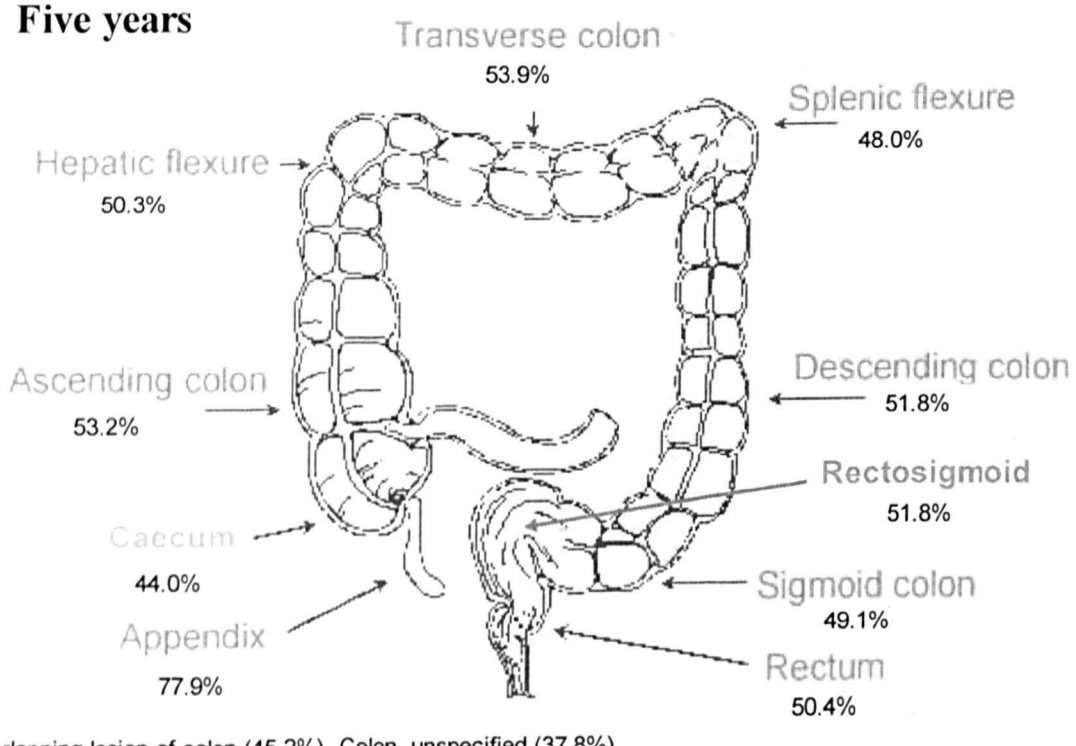
Within the colon, relative survival at one year after diagnosis was highest for distal tumours (descending colon, rectosigmoid, sigmoid colon and rectum) and cancer of the appendix (Figure 6.4). At five years after diagnosis, relative survival was highest for cancers of the ascending, transverse and descending colon, rectosigmoid and appendix. For colon cancer the narrowest deprivation gap in survival at five years between affluent and deprived was 13.5% for the appendix but was widest at 21.0% for the sigmoid colon. There were only 202 cancers of the appendix, mostly in young patients (52% under age 55).

Further analysis will be based on the wider groupings of colon, rectosigmoid and rectum because they are more widely used and identify the main associations between deprivation and survival. Additionally, the large proportion of colon cancers without a specific site makes interpretation difficult.

Figure 6.4: Relative survival (%) at one and five years after diagnosis by specific colorectal cancer site: colorectal cancer patients diagnosed 1997-2004, North West of England



Overlapping lesion of colon (63.0%), Colon, unspecified (52.0%)



Overlapping lesion of colon (45.2%), Colon, unspecified (37.8%)

Subsite

Colon cancer patients had lower survival at one year than rectal cancer patients, however this reversed for conditional five year survival with survival lower in rectal cancer patients than colon (Table 6.7). Rectosigmoidal cancers had survival in between colon and rectal cancer for both one year and conditional five year survival.

Colon, rectosigmoid and rectal cancer patients had very similar deprivation gaps in survival at one year (1.34, 1.35, 1.32, respectively). For rectal and rectosigmoidal cancer the socioeconomic inequalities in survival in five year conditional survival were similar to those found in one year survival. There were no significant inequalities in colon cancer survival for five year conditional survival. The difference in survival inequalities after the first year of diagnosis for colon, rectosigmoidal and rectal cancer may be attributed to differences in treatment and time to cure; colon cancer has higher post-operative mortality and excess mortality in the first year, reaching statistical 'cure' earlier.[12]

Grade

Higher grade was associated with lower survival but this was largely explained by the close association between advanced stage and high grade. The excess hazard of death for grade IV compared to grade I decreased by almost half after adjustment for stage from 3.89 (95% 2.98, 5.09) to 2.13 (95% 1.64, 2.77) after adjustment for stage and age (data not shown).

Inequalities in survival during the first year after diagnosis were similar for all grades (1.24 to 1.38) (Table 6.5). Contrary to the trends seen for stage and age, increasing grade was associated with an increase in the socioeconomic inequalities for conditional five year survival (Table 6.6). As with grade-specific survival the deprivation gaps may be strongly influenced by stage. Additionally, there were very small numbers of patients in grade III (14%) and grade IV (0.3%) resulting in inconsistent trends over socioeconomic groups at one year and socioeconomic-specific estimates not possible for five year conditional survival.

Histology

Adenocarcinoma was the most common histological type (90.5%) and had the highest survival at five years after diagnosis (Table 6.3). Mucinous and serous cancers had better survival than adenocarcinomas at one year (Table 6.7) but conditional five year

survival was lower. Factors associated with a poorer prognosis, such as advanced stage (10.0% in stage IV) and higher grade tumours (16.5% in grade IV), were more common for muscinous and serous cancers.

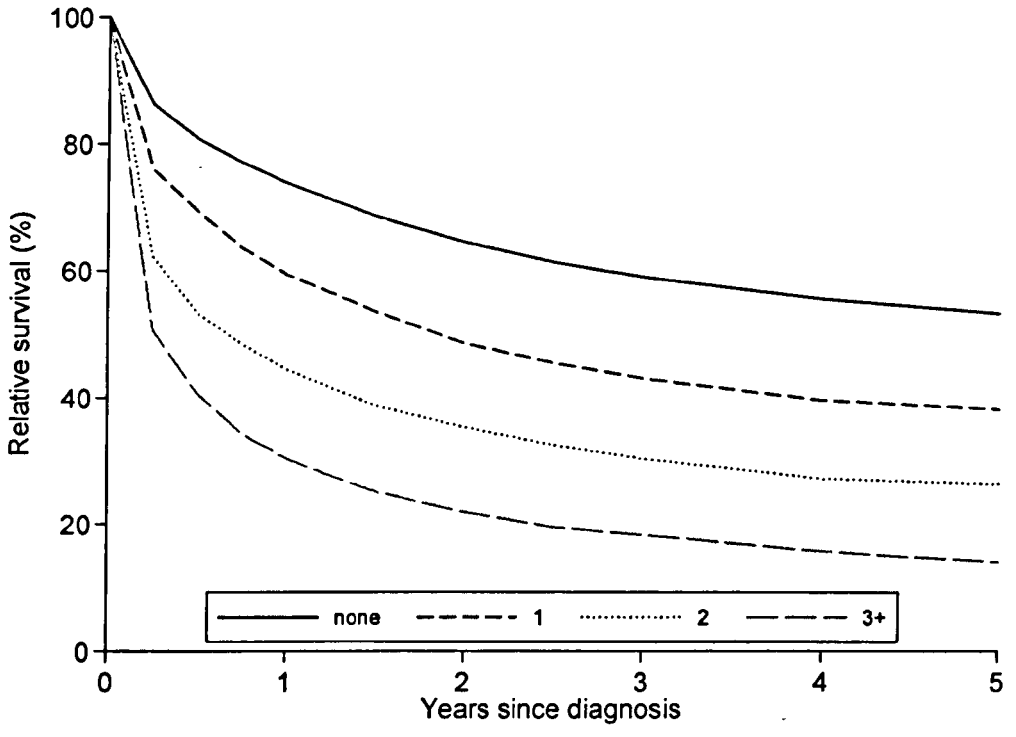
The one year deprivation gap in survival was similar for adenocarcinoma and mucinous or serous cancers (Tabel 6.5). There were only socioeconomic inequalities in five year conditional survival for adenocarcinoma (Table 6.6). There were no significant socioeconomic variations in survival for other specified histological types at for one year or five year conditional on survival.

Comorbidity

Increasing levels of comorbidity were associated with a decrease in survival (Figure 6.5). At five years after diagnosis patients with a comorbidity level of 3 or more had excess hazard of death at five years of 4.11 (95% CI 3.77, 4.48), compare to patients with no comorbidity. Higher levels of comorbidity were associated with increasing deprivation, age and stage. After adjusting for deprivation, age and stage the excess hazard of death for patients with a comorbidity score of 3 or more decreased to 2.45 (95% CI 2.22, 2.70) (see Table 5.1 & 5.6).

At one year after diagnosis the socioeconomic inequalities in survival were similar for most levels of comorbidity (EHR 1.25 to 1.33), with the exception of patients with a comorbidity level of one (EHR 1.09). The deprivation gap in survival was narrower for five year conditional survival for patients with a comorbidity level of one, but increased after the first year (EHR 1.31). Patients with a comorbidity level of one had single comorbidity with low severity weight (see Appendix 4.3), which may have had a larger effect on mortality after the first year of diagnosis (i.e. chronic, rather than acute). Inequalities in survival at five years conditional on surviving the first year, occurred for each comorbidity level although they were highest for patients with a comorbidity level of 3 or more.

Figure 6.5: Relative survival (%) up to five years after diagnosis for each level of Charlson measure (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England



Impact of clinical and demographic variables on the deprivation gap

There were substantial socioeconomic inequalities in survival at one year after diagnosis but socioeconomic inequalities narrowed substantially for patients who survived the first (Table 6.8). In the first year after diagnosis, adjusting for age and comorbidity had the biggest impact on narrowing the deprivation gap (EHR adjusted for age 1.37; adjusted for age and comorbidity 1.34). Stage explained some of the excess hazard of death in the first year after diagnosis decreasing the excess hazard ratio from 1.41 (unadjusted) to 1.38. Together age, stage and comorbidity were strongly correlated and decreased the excess mortality at one year (excess mortality for deprived: 1.36 95% CI 1.26, 1.46). The addition of subsite, sex, grade and histology did not further explain the deprivation gap compared to the age, stage and comorbidity model. The fully adjusted model explained very little of the deprivation gap with an excess hazard of 1.37 (95% CI 1.28, 1.48). Between two and five years after diagnosis there were no significant deprivation gaps in any of the models.

Table 6.8: The impact adjusting for each variable on the excess hazard ratio of death by deprivation group (reference = affluent) (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

	one year			two to five year			
	EHR			EHR			
		95% CI			95% CI		Significance level
		lower	upper		lower	upper	
adjusted for follow-up time							
Deprivation group							
1 - affluent	1.00	-	-	1.00	-	-	
2	1.05	0.97	1.14	1.00	0.90	1.11	Interaction of time (<= 1 year, >1 year) pvalue=0.0047
3	1.23	1.13	1.33	1.01	0.91	1.13	
4	1.31	1.21	1.42	1.12	1.01	1.25	
5 - deprived	1.41	1.32	1.52	1.16	1.05	1.28	
Age and follow-up time							
Deprivation group							
1 - affluent	1.00	-	-	1.00	-	-	
2	1.03	0.95	1.12	0.99	0.89	1.09	Adjustement for age p<0.001‡
3	1.18	1.09	1.27	0.98	0.89	1.09	
4	1.25	1.16	1.35	1.08	0.98	1.20	
5 - deprived	1.37	1.28	1.47	1.13	1.02	1.24	
Age, comorbidity and follow-up time							
Deprivation group							
1 - affluent	1.00	-	-	1.00	-	-	
2	1.04	0.96	1.13	0.99	0.90	1.10	Adjustment for comorbidity p<0.001‡
3	1.17	1.08	1.27	1.00	0.90	1.11	
4	1.24	1.15	1.34	1.09	0.99	1.21	
5 - deprived	1.34	1.25	1.44	1.13	1.02	1.24	
Age, stage and follow-up time							
Deprivation group							
1 - affluent	1.00	-	-	1.00	-	-	
2	1.06	0.97	1.15	1.01	0.91	1.12	Adjustment for stage p<0.001‡
3	1.18	1.09	1.28	0.99	0.89	1.10	
4	1.26	1.17	1.36	1.10	1.00	1.22	
5 - deprived	1.38	1.29	1.48	1.14	1.03	1.25	
Age, stage, comorbidity and follow-up time							
Deprivation group							
1 - affluent	1.00	-	-	1.00	-	-	
2	1.06	0.97	1.15	1.01	0.91	1.12	Adjustment for comorbidity p<0.001‡
3	1.18	1.08	1.27	1.00	0.90	1.11	
4	1.25	1.16	1.35	1.11	1.00	1.23	
5 - deprived	1.36	1.26	1.46	1.14	1.03	1.25	
Age, stage, comorbidity, histology, grade, subsite, sex and follow-up time							
Deprivation group							
1 - affluent	1.00	-	-	1.00	-	-	
2	1.07	0.98	1.16	1.02	0.92	1.13	Adjustment for histology, grade, subsite and sex p<0.001‡
3	1.18	1.09	1.28	1.01	0.91	1.12	
4	1.26	1.16	1.36	1.12	1.01	1.24	
5 - deprived	1.37	1.28	1.48	1.15	1.05	1.27	
Age, stage, comorbidity, histology, grade, subsite, sex and follow-up time, interation between stage and follow-up time and age and follow-up time							
Deprivation group							
1 - affluent	1.00	-	-	1.00	-	-	
2	1.05	0.96	1.14	1.03	0.93	1.15	Fully adjusted p<0.001‡
3	1.15	1.07	1.25	1.03	0.93	1.15	
4	1.22	1.14	1.33	1.15	1.04	1.28	
5 - deprived	1.34	1.25	1.44	1.17	1.06	1.29	

‡ Significance level of additional variable compared to previous model

Lower survival was associated with increasing levels of stage, age, grade, comorbidity and deprivation, with deprivation having the weakest association of these (Table 6.7).

The inequality in the excess hazard ratio for the deprived was particularly high in the first year after diagnosis (1.34 95% CI 1.23, 1.46) than in subsequent years (1.16 95% CI 1.05, 1.29) (Table 6.8). The excess hazard was higher at one year than for conditional excess hazard for all variables except subsite, stage and mucinous or serous histology. After adjustment for all factors and non-proportionality the deprivation gap was wider than in the unadjusted one year and conditional survival models. There was a significant excess hazard for deprived patients in the fully adjusted model at one year (1.34 95% CI 1.25, 1.44) but not at two to five years after diagnosis.

Age at diagnosis and stage had the strongest impact on survival, although age was not significant at two to five years in the fully adjusted model (which included interactions with time) (data not shown). The fully adjusted model decreased the excess hazard for deprivation, age and stage at one year and two to five years (compared to conditional). Adjustment for all factors, after imputing missing data, only accounted for a small proportion of the socioeconomic inequalities in colorectal cancer survival at one year after diagnosis but fully explained the inequalities after the first year of diagnosis.

Colon cancer patients had lower relative survival than rectosigmoid or rectal cancer. Factors associated with a poor prognosis were higher in colon patients such as unspecified histology, aged over 75 at diagnosis, and men but there was no significant difference in deprivation, stage or grade.

Summary

The deprivation gap in survival at one year after diagnosis was substantial and it was only slightly moderated by adjustment for clinical (stage, grade, histology, comorbidity, subsite) and demographic variables (age, sex). For patients who survived the first year after diagnosis, there was no significant difference in survival between those from affluent and deprived backgrounds for most categories. Inequalities in survival were generally wider for factors associated with a good prognosis, such as early stage at diagnosis and low grade (highly differentiated). There were no socioeconomic differences in stage at diagnosis, although more deprived patients generally had more comorbidity. Comorbidity was associated with poor survival but the deprivation gap was not substantially narrowed by adjustment for comorbidity or any other factors.

The presence of a significant deprivation gap in the first year indicates that the cause(s) of the deprivation gap are associated with factors particularly related to the first year after diagnosis. Variations in access to treatment and post-operative mortality may particularly influence survival in the first year, although curative treatment will influence longer-term survival. These issues will be explored in the next two chapters.

(1) Coleman MP, Rachet B, Woods LM, Mitry E, Riga M, Cooper N, Quinn MJ, Brenner H, Estève J. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *British Journal of Cancer.* 2004; 90:1367-1373.

(2) Coleman MP, Babb P, Damiecki P, Grosclaude P, Honjo S, Jones J, Knerer G, Pitard A, Quinn M, Sloggett A, De Stavola B. *Cancer survival trends in England and Wales, 1971-1995: deprivation and NHS Region. (Studies in Medical and Population Subjects No. 61).* London: The Stationery Office, 1999.

(3) Shack LG, Rachet B, Brewster DH, Coleman MP. Socioeconomic inequalities in cancer survival in Scotland 1986-2000. *British Journal of Cancer.* 2007; 97:999-1004.

(4) Schrijvers C, Coebergh J, Mackenbach JP. Socioeconomic status and comorbidity among newly diagnosed cancer patients. *Cancer.* 1997; 80:1482-1488.

(5) De Marco MF, Janssen-Heijnen MLG, van der Heijden LH, Coebergh JWW. Comorbidity and colorectal cancer according to subsite and stage: a population-based study. *European Journal of Cancer.* 2000; 36:95-99.

(6) Brewster DH, Thomson CS, Hole DJ, Black RJ, Stroner PL, Gillis CR. Relation between socioeconomic status and tumour stage in patients with breast, colorectal, ovarian and lung cancer: results from four national, population based studies. *British Medical Journal.* 2001; 322:830-831.

(7) Ionescu MV, Carey F, Tait IS, Steele RJC. Socioeconomic status and stage at presentation of colorectal cancer. *Lancet.* 1998; 352:1439.

(8) Green J, Watson J, Roche M, Beral V, Patnick J. Stage, grade, and morphology of tumours of the colon and rectum recorded in the Oxford Cancer Registry, 1995-2003. *British Journal of Cancer.* 2007; 96:140-142.

(9) Rubin DB. Multiple imputation after 18+ years. *Journal of the American Statistical Association.* 1996; 91:473-490.

(10) Wichmann MW, Ayala A, Chaudry IH. Male sex steroids are responsible for depressing macrophage immune function after trauma-hemorrhage. *American Journal of Physiology.* 1997; 273:13335-1340.

(11) Angele MK, Knöferl MW, Ayala A, Cioffi WG, Bland KI, Chaundry IH. Male and female sex steroids: do they produce deleterious or beneficial effects on immune responses after trauma and hemorrhage? *Surgical Forum.* 1998; 49:43-45.

(12) Lambert PC, Dickman PW, Osterlund P, Andersson T, Sankila R, Glimelius B. Temporal trends in the proportion cured for cancer of the colon and rectum: a population-based study using data from the Finish Cancer Registry. 2007.

Chapter 7

Are there socioeconomic variations in colorectal cancer treatment?

Overview

Treatment regimes, particularly surgery, are mainly determined by clinical factors, such as stage at diagnosis. Not surprisingly treatment is also strongly associated with survival. Geographic variations in the quality and type of treatment received, described in the popular media as the 'postcode lottery', are known to exist in the UK, and these may have contributed to socioeconomic gradients in survival. These geographic variations primarily influence the availability of chemotherapy drugs, however there are also variations in surgical type and quality by hospital and/or surgeon.[1] Surgical outcomes are better when patients are treated by specialist colorectal surgeons, by surgeons with high colorectal case-loads and at high-volume hospitals[2-5] but deprived patients may be less likely to receive surgery under these conditions. Inequalities in access, type and quality of treatment could contribute to inequalities in survival, but it remains unclear if patients from deprived and affluent backgrounds do receive similar treatment, after clinically relevant factors are taken into account.

Aims

Socioeconomic inequalities in the type and quality of treatment received for colorectal cancer patients in the North West of England diagnosed between 1997 and 2004 were evaluated, after adjusting for clinical and demographic factors. In the previous chapter, socioeconomic inequalities, particularly in the first year after diagnosis, could not be explained by clinical or demographic factors. In this chapter, differences in treatment receipt between deprived and affluent will be assessed after taking into account clinical and demographic factors thus providing the basis for assessing socioeconomic variations in survival and treatment (Chapter 8). The impact of multiple imputation for missing data on the distribution of patients receiving surgery, chemotherapy and radiotherapy, and hospital and surgeon volume will first be evaluated. Secondly, treatment regimes will be analysed separately for colon and rectal cancer, because of differences in surgery type, treatment regimes and outcome were evaluated. Socioeconomic variations in the type of surgery received will be evaluated, particularly for anterior resection in rectal cancer patients. Variations in hospital and surgical volume were also evaluated as 'proxy' measures of surgical quality and surgeon experience. Treatment in accordance with clinical guidance improves survival and

decreases reoccurrence.[6,7] A crude measure of whether treatment was in accordance with stage-specific guidelines was also evaluated.

The analysis presented in this chapter will mainly be based on data after imputation, unless otherwise specified.

Imputation

Treatment

Despite the use of both cancer registry and HES data information on treatment was incomplete. Missing treatment data were imputed separately for surgery, chemotherapy and radiotherapy and combined after imputation to create eight treatment regimes; surgery only; surgery and chemotherapy; surgery and radiotherapy; surgery and chemoradiotherapy; chemotherapy only; radiotherapy only; chemoradiotherapy; and no treatment. In the original data increasing deprivation was strongly associated with missing treatment (missing surgery, chemotherapy and radiotherapy) and was strongly associated with missing data for other clinical and demographic variables (e.g. stage, age, comorbidity). The biggest contributor to missing treatment in deprived patients was chemotherapy, which was received by only 16.0% of deprived patients and 20.5% of affluent patients (missing for deprived 64.6%; affluent 60.0%).

In the original dataset increasing age and more advanced stage were strongly associated with non-surgical treatment regimes (and missing treatment information), both before and after adjustment for clinical and demographic factors (see Table 3.16). Lower levels of surgery, radiotherapy and/or chemotherapy might be expected in elderly patients or for patients with advanced stage who may be too frail to endure invasive procedures, or for whom treatment would not be curative. The association between older age, more advanced stage and missing treatment data in the original dataset was partially explained by the interaction of age and stage, but it persisted even after adjustment for sex, deprivation, histology, subsite and year of diagnosis. For example, the unadjusted odds ratio for missing treatment data for patients aged 85 to 99 was 9.8 (95% CI 7.2, 13.4) and but fell to 5.8 (95% CI 4.1, 8.2) after adjustment.

High grade and unknown grade were associated with missing surgery, chemotherapy and radiotherapy. This association is probably because of lack of pathology (and no surgery occurred). Additionally, missing grade and unknown grade would be associated with a poor prognosis and a 'true' lack of active treatment.

Surgical treatment was the most common (and complete) treatment both in the original data (81.9%) and after (90.4%) imputation (Table 7.1). The recorded proportion of patients given chemotherapy was low and as a result imputation had the biggest impact on chemotherapy. Chemotherapy is the most difficult treatment information for cancer registries to obtain because it is rarely recorded in electronic datasets. Frequently chemotherapy is prescribed at non-specialist hospitals or off-site clinics run by the specialist centre, which makes access to case notes or electronic datasets difficult. HES linkage was used to improve the completeness of chemotherapy and surgery data. However, the linkage improved surgery more than chemotherapy.

Radiotherapy treatment is given at only three centres in the North West. Each centre provided radiotherapy treatment information directly to the cancer registry thereby achieving higher completeness than chemotherapy or surgery (see chapter 4). In the original dataset radiotherapy was missing for 19.7% of colorectal patients, but was more complete for rectal (16.0% missing) than colon cancers (21.1% missing); radiotherapy is not normally provided for colon cancer patients. After imputation radiotherapy was substantially more common for rectal cancer patients (including rectosigmoid) (38.2%) than colon cancer patients (6.2%).

The cancer registry shifted toward obtaining information from electronic data sources and away from reviewing patient case notes to obtain treatment information between 1997 and 2004 (see Table 3.16). This shift away from case note review and toward electronic datasets, correlated with a decrease in the proportion of patients with complete treatment over time. Electronic datasets designed for recording all patients (i.e. non-cancer and cancer patients) rarely record detailed cancer treatment and stage.

Table 7.1: Distribution (%) of surgery, chemotherapy and radiotherapy for patients with known (original 'complete' data) treatment and data after imputation: colorectal cancer patients diagnosed 1997-2004, North West of England

	Complete						Imputed	
	Treatment		No treatment		Missing*		Treatment	No treatment
	No.	%	No.	%	No.	%	%	%
Surgery	24,220	81.9	2,703	9.1	2,640	8.9	90.4	9.6
Chemotherapy	5,253	17.8	5,429	18.4	18,881	63.9	51.1	48.9
Radiotherapy	3,061	12.5	3,684	67.9	5,818	19.7	17.0†	83.0

*Treatment was assumed to be missing if there was no record of treatment in registry or HES and the patient could not be linked to any HES records.
†34.3% of rectal (and rectosigmoidal) cancer patients had radiotherapy

Surgery only, followed by surgery and chemotherapy were the most common treatment regimes, both in the original data and after imputation (after imputation 39.2% and 35.5%, respectively) (Table 7.2). The third most common regime shifted from surgery and radiotherapy in the original dataset to surgery and chemoradiotherapy after imputation, because the proportion of patients receiving chemotherapy increased substantially after imputation (see Table 6.1). These treatment regimes correspond to clinical guidance recommending that patients with early stage colon and rectal cancers receive surgery only, with moderate stages (stage II or III) receiving surgery and chemotherapy for colon cancer and surgery and chemoradiotherapy for rectal cancer.[8,9] The proportion of patients receiving no treatment increased slightly after imputation to 8.5% from 8.2% in the original dataset and was higher in deprived patients in both imputed and original datasets. Very few patients had chemotherapy and radiotherapy either alone or in combination (without surgery). Patients with missing treatment data for all three modalities (no surgery, chemotherapy and radiotherapy) were associated with poorer prognostic factors and were more likely to have no treatment (61.7%) or surgery only (21.4%) after imputation (Table 7.2). Treatment without surgery is generally palliative thus it is unsurprising that after imputation no treatment (no surgery, chemotherapy or radiotherapy) and non-surgical treatment were associated with poor prognostic factors, such as older age and advanced stage.

Table 7.2: Distribution (%) of known (original), missing and imputed data by treatment regime: colorectal cancer patients diagnosed 1997-2004, North West of England

		Imputed data	
	Complete' data (%) (patients with no missing data)	Patients with missing treatment (%)	All patients (%)
Treatment			
surgery only	63.8	21.4	39.2
surgery and chemotherapy	12.2	12.4	35.1
surgery and radiotherapy	7.3	0.3	0.8
surgery and chemoradiotherapy	4.3	4.2	15.3
chemotherapy only	1.9	0.1	0.4
chemoradiotherapy	0.7	<0.05	0.3
radiotherapy only	1.1	<0.05	0.4
no treatment	8.8*	61.7	8.5

In the original dataset deprived patients were more likely than affluent patients to have surgery only, or no treatment, and were less likely to receive adjuvant therapy. These inequalities widened after imputation (Table 7.3). The association between increasing deprivation and lack of treatment was stronger after imputation, although it is difficult to directly compare untreated patients before and after imputation. In the original data patients were assumed to have no treatment if they had no known surgery, radiotherapy and chemotherapy, but surgery, chemotherapy and radiotherapy were imputed separately and then combined to create an amalgamated record with the best available data on treatment (see chapter 4). Therefore, an imputed treatment for each of surgery, chemotherapy or radiotherapy could substantially change the distribution of the combined treatment regimes.

Table 7.3: Distribution (%) of treatment regime by deprivation in the original data and data after imputation: colorectal cancer patients diagnosed 1997-2004, North West of England

	Original "complete" data						Imputed					
	1 - affluent	2	3	4	5 - deprived	all	1 - affluent	2	3	4	5 - deprived	all
Clinical factors												
Treatment												
surgery only	62.2	62.7	64.8	63.5	65.1	**63.8**	36.6	36.7	39.6	40.2	41.3	**39.2**
surgery and chemo	14.2	14.0	10.8	12.0	11.0	**12.2**	37.2	37.8	34.6	33.9	33.2	**35.1**
surgery and radiotherapy	7.5	7.1	7.64	7.7	6.9	**7.3**	1.0	0.8	0.7	0.9	0.8	**0.8**
surgery and chemoradio	4.4	4.4	3.9	4.5	4.2	**4.3**	16.0	15.5	15.5	15.6	14.7	**15.3**
chemotherapy only	2.0	2.0	2.0	1.8	1.7	**1.9**	0.5	0.4	0.3	0.3	0.4	**0.4**
radiotherapy only	0.9	0.6	0.6	0.7	0.5	**0.7**	0.5	0.3	0.3	0.3	0.2	**0.3**
chemoradiotherapy	1.1	0.9	1.2	1.1	1.1	**1.1**	0.7	0.4	0.3	0.4	0.2	**0.4**
no treatment	7.7	8.3	9.0	8.7	9.6	**8.8**	7.5	8.1	8.8	8.4	9.3	**8.5**
missing	(4.5)	(5.8)	(6.3)	(7.2)	(7.7)	**(6.5)**						
	100.0	100.0	100.0	100.0	100.0	**100.0**	100.0	100.0	100.0	100.0	100.0	**100.0**

Hospital volume

The overall distribution of surgeon volume or hospital volume was similar in the original dataset and after imputation. After imputation most patients received surgery at a high- or very high-volume hospital, by a moderate- to low-volume surgeon (Table 7.4). Surgeon volume and hospital volume were imputed for patients known to have received surgery (for which surgeon and/or hospital volume were missing) or estimated to have received surgery after imputation (see chapter 4). Most patients with missing surgery data were estimated not to have had surgery after imputation. A large proportion of patients with missing data on hospital volume in the original dataset were imputed not to have had surgery and thus no hospital of surgery volume (37.2%).

In the original dataset, 24.8% of patients had missing data on hospital volume, while only 18.3% of patients had missing data on surgeon volume. The difference in completeness of hospital and surgery volume data were because 10.7% of patients had the place of surgery recorded as primary acute trust or primary care trust, rather than a specific hospital (e.g. Pennine Acute Trust, rather than one of the four hospitals within the trust).

Private hospitals conducted only 2.4% of the surgery (0.4% in the original dataset) with most of these patients resident in affluent areas (see Table 6.1). Colorectal cancer patients treated in the private sector were generally younger at diagnosis, diagnosed at an earlier

stage and had lower levels of comorbidity than colorectal cancer patients treated at NHS hospitals.

Table 7.4: Distribution (%) of known (original), missing and data after imputation by surgeon and hospital volume (colorectal surgeries per year): colorectal cancer patients diagnosed 1997-2004, North West of England

			Imputed data	
		Original 'complete' data (%) (patients with no missing data)	Patients missing surgery, chemotherapy and radiotherapy (%)	All patients (%)
Hospital volume				
		(n=20,938)	(n=8,625)	
very high	(over 150)	23.2	18.7	26.2
high	(100 to 149)	31.4	24.9	35.4
moderate	(50 to 99)	17.5	13.7	19.6
low	(less than 50)	2.8	4.0	5.9
Private		0.4	1.6	2.4
none*		24.8	37.2	10.5
Surgeon volume				
		(n=20,467)	(n=9,096)	
very high	(over 60)	2.7	1.9	2.9
high	(40 to 60)	14.4	10.3	15.7
moderate	(20 to 39)	30.7	23.1	32.7
low	(less than 20)	33.9	30.2	38.2
none*		18.3	34.4	10.6

*Includes patients with no surgery for complete analysis and no known or imputed surgery for imputed analysis

Surgeon volume

Imputation did not substantially alter the distribution of patients who had their surgery conducted by a moderate- or low-volume surgeon (Table 7.4). As described previously in relation to hospital volume, a large proportion of patients with missing surgeon also had missing surgery status. After imputation most patients with missing surgeon in the original data were estimated not have undergone surgery (34.4%). After imputation the proportion of patients who had their surgery conducted by a low-volume surgeon increased (33.9%, to 38.2%). Patients who had missing surgeon volume in the original data generally had a poorer prognosis so it is logical that they might have non-curative or emergency surgery from a low-volume surgeon.

Analysis of data after imputation, complete data and data with a category for missing data had very similar excess hazard ratios of death for both surgeon and hospital volume (Table 6.3). The only substantial difference after imputation was an increase in the excess hazard for patients who received no surgical treatment and for whom obviously, no surgeon or hospital volume analysis could be done. Variations in survival and treatment patterns will be discussed in chapter 8.

Access to treatment

Treatment

The proportion of patients receiving surgery (of any kind) slightly decreased with increasing deprivation, from 89.5% for affluent patients to 87.8% for deprived patients (Table 7.5). After adjustment for clinical and demographic factors, however increasing deprivation was associated with a higher odds ratio of receiving surgery (deprived odds ratio 1.63). This suggests that deprived patients generally have higher levels of clinical and demographic factors that may be contra indicators for surgery than affluent patients. This may highlight the large influence of clinical and demographic factors as contra indicators of surgery.

The proportion of rectal cancer patients receiving radiotherapy decreased slightly with increasing deprivation but this was explained by variations in clinical and demographic factors (OR for deprived: 0.90, 95% CI 0.77, 1.04). Deprived patients were less likely to receive chemotherapy treatment and this could not be explained by associations with clinical and demographic factors (OR for deprived: 0.84). These socioeconomic trends in surgery and radiotherapy highlight the higher levels of factors which may be potential contra-indicators for treatment (e.g. comorbidity, age) in deprived patients, and the importance of imputing missing data and then fully adjusting for these factors in the analysis. The lack of significant socioeconomic variation in chemotherapy may be because of the impact of imputing data with such a large proportion missing.

Over 99% of patients with no comorbidity received surgery compared with only 6% of patients with a comorbidity score of 3 or more (Table 7.5). Older age was also associated

with a decrease in the proportion of patients receiving surgery after age 75, but this was explained by variations in clinical and demographic factors (OR 2.78 and 1.85). Patients aged between 55 and 84 were significantly more likely to have surgery after adjusting for clinical and demographic factors (compared to 15 to 44 year olds). Increasing age and comorbidity were both independently associated with a rapid decrease in chemotherapy and radiotherapy provision. The lower prevalence of chemotherapy and radiotherapy may suggest that surgery in older patients were not intended as curative.

Advanced stage was negatively associated with surgical treatment. Conversely, advanced stage was positively associated with chemotherapy or radiotherapy probably because they were received actively in moderate to advanced stages (Stage II and III) and palliatively for advanced disease (stage IV). Radiotherapy was significantly more likely to be received by rectal cancer patients, as it is the current recommended guidance.

Table 7.5: Distribution (%) and adjusted odds ratios for receiving surgery, chemotherapy and radiotherapy by clinical and demographic variables (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

	Surgery (reference = surgery)				Chemotherapy (reference = chemotherapy)				Radiotherapy* (reference = radiotherapy)			
		Odds Ratio†				Odds Ratio†				Odds Ratio†		
			95% CI				95% CI				95% CI	
	%		lower	upper	%		lower	upper	%		lower	upper
overall	90.4	-			51.1	-			17.0	-		
sex												
men	91.6	1.00	-	-	55.9	1.00	-	-	20.0	1.00	-	-
women	89.0	0.54	0.43	0.67	45.0	0.76	0.70	0.82	13.2	0.80	0.72	0.89
age												
15 to 44	92.9	1.00	-	-	73.0	1.00	-	-	30.2	1.00	-	-
45 to 54	94.4	1.45	0.65	3.24	76.6	1.18	0.88	1.58	31.2	0.89	0.64	1.24
55 to 64	93.2	2.13	1.03	4.37	69.5	0.84	0.65	1.09	26.2	0.67	0.49	0.91
65 to 74	92.9	2.89	1.43	5.86	57.7	0.51	0.40	0.66	18.4	0.47	0.35	0.64
75 to 84	88.8	2.78	1.37	5.62	36.3	0.23	0.18	0.29	9.7	0.25	0.18	0.34
85 to 99	79.4	1.85	0.89	3.83	17.2	0.09	0.07	0.12	3.8	0.09	0.06	0.14
deprivation												
1 - affluent	89.5	1.00	-	-	54.5	1.00	-	-	18.2	1.00	-	-
2	89.0	1.14	0.78	1.67	54.0	1.05	0.92	1.20	17.1	1.00	0.85	1.18
3	88.5	1.34	0.93	1.94	50.6	0.97	0.85	1.11	16.8	1.00	0.85	1.18
4	88.5	1.47	1.02	2.11	50.2	0.95	0.84	1.08	17.3	1.04	0.89	1.23
5 - deprived	87.8	1.63	1.17	2.26	48.3	0.84	0.74	0.94	16.1	0.90	0.77	1.04
subsite												
colon	89.6	1.00	-	-	48.1	1.00	-	-	6.2			
rectosigmoid	93.9	1.36	0.88	2.11	54.4	1.10	0.96	1.27	19.5	-		
rectum	91.2	0.81	0.63	1.03	56.3	1.29	1.18	1.41	38.2	-		
stage												
I	96.2	1.00	-	-	45.7	1.00	-	-	14.8	1.00	-	-
II	94.4	0.76	0.49	1.19	48.3	1.33	1.17	1.52	14.3	1.52	1.30	1.78
III	87.7	0.29	0.19	0.45	54.7	1.88	1.65	2.14	19.5	2.21	1.89	2.58
IV	72.0	0.10	0.06	0.18	49.5	1.73	1.38	2.16	18.3	2.31	1.72	3.09
comorbidity												
none	99.3	1.00	-	-	55.8	1.00	-	-	18.4	1.00	-	-
1	76.0	0.02	0.01	0.03	40.3	0.64	0.53	0.78	11.2	0.63	0.47	0.84
2	22.5	<0.01			16.2	0.15	0.12	0.19	7.8	0.32	0.24	0.43
3+	6.0	<0.01			6.9	0.07	0.05	0.09	4.2	0.18	0.12	0.29

*Analysis for radiotherapy was limited to rectosigmoid and rectal cancers
†Adjusted for all variables in table

The combination of surgery, chemotherapy and radiotherapy in treatment regimes is a more clinically relevant description of treatment, since clinical guidance recommends specific treatment regimes. The following section combines individual treatments into treatment regimes.

Treatment regimes

Most patients receive surgery (90.4%), either alone (39.2%) or in combination with chemotherapy (35.1%) or chemoradiotherapy (15.3%) (Table 7.6). The proportion of patients treated with chemotherapy only, chemoradiotherapy only or radiotherapy only

were lower in the deprived than the affluent, but there was a very small proportion of patients treated with these regimes, regardless of socioeconomic status. Deprivation was positively associated with treatment by surgery only, and inversely associated with treatment with both surgery and chemotherapy, and surgery and radiotherapy (Table 7.7). Surgery was evaluated as a binary variable (yes/no) but will in fact be a heterogeneous group with regard to surgical type (e.g. emergency, non-emergency) and intent (curative and non-curative). Patients treated with surgery only for early-stage colorectal cancer may be treated with curative intent, whereas treatment by surgery alone for advanced stage is generally palliative (e.g. debulking). The higher proportion of deprived than affluent patients receiving surgery alone after adjustment may be due to differences in the type and intent of surgery. Stage at diagnosis after imputation was the same between affluent and deprived patients, possibly suggesting that curative surgery and the type of surgery should be similar between socioeconomic groups. However, deprived patients did have higher levels of comorbid conditions than affluent patients possibly suggesting that a larger proportion of the surgical procedures in deprived patients may be non-curative, either because the comorbidity is a contra-indicator for surgery or life expectancy is perceived to be limited by comorbidity. However, the lack of specificity of coding (e.g. TME), lack of specific surgical information (e.g. curative, emergency) and the necessity to impute missing surgery data made it impossible to sub-divide surgery in these analyses. There was also a higher proportion of deprived patients receiving no treatment (no surgery, chemotherapy or radiotherapy), but this was explained by associations with stage, comorbidity, age, subsite and sex (Table 7.6 and 7.7).

Increasing comorbidity was very strongly associated with a lack of treatment, and consequently negatively associated with other treatment regimes (Table 7.7). Comorbid conditions may limit the possibility of offering some treatments, particularly surgery. Advanced stage also influences treatment options with chemotherapy, radiotherapy and adjuvant therapy becoming more common. Increasing stage was associated with a decrease in surgery only, and in no treatment, but increasing proportions of patients who were treated with surgery and adjuvant therapy (chemotherapy and chemoradiotherapy).

Women were less likely than men to receive surgery, chemotherapy or radiotherapy, but women had slightly better survival at five years (EHR for women compared to men: 0.89 95% CI 0.80, 0.99). Men were more likely to receive adjuvant therapy than women whilst women were more likely to have surgery only, or no treatment, which may suggest that treatment for some is focused on those who are most likely to benefit from treatment. Men were more likely to have rectal cancer than women but even after adjustment for subsite, age and other clinical factors, women had slightly better survival.

Lower levels of adjuvant therapy and higher proportions of surgery only were associated with increasing age (Table 7.6). The high proportion of surgery only in older patients is probably attributed to more non-curative surgeries, with this hypothesis supported by the consequently lower levels of adjuvant treatment. A substantially higher proportion of older patients received no treatment but this was explained by factors such as advanced stage, and comorbidity (Table 7.7).

Colon cancer patients were most likely to receive surgery only or surgery and chemotherapy while rectal cancer patients were most likely to received surgery only or surgery and chemoradiotherapy (Table 7.6). Patients with a rectosigmoidal cancer had a distribution of treatment that was intermrdiate between both rectal and colon cancers.

Table 7.6: Distribution (%) of treatment regime by clinical and demographic variables (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

	surgery only	surgery and chemotherapy	surgery and radiotherapy	surgery and chemoradio therapy	radiotherapy only	chemotherapy only	chemoradio therapy only	no treatment
overall	39.2	35.1	0.8	15.3	0.4	0.3	0.4	8.5
sex								
men	35.6	36.9	0.8	18.3	0.4	0.3	0.4	7.3
women	43.8	32.8	0.8	11.6	0.3	0.3	0.4	10.0
age								
15 to 44	21.1	43.3	0.3	28.2	0.6	0.3	1.1	5.2
45 to 54	18.7	46.0	0.7	29.1	0.4	0.5	1.1	3.6
55 to 64	24.2	44.1	0.7	24.3	0.5	0.5	0.7	5.2
65 to 74	35.0	40.3	0.9	16.7	0.4	0.3	0.4	6.0
75 to 84	51.8	27.7	0.9	8.3	0.3	0.1	0.2	10.7
85 to 99	61.4	14.4	0.8	2.8	0.2	0.1	<0.1	20.3
deprivation								
1 - affluent	36.6	37.3	1.0	16.0	0.5	0.5	0.7	7.5
2	36.7	37.8	0.8	15.5	0.4	0.3	0.4	8.1
3	39.6	34.6	0.7	15.5	0.3	0.3	0.3	8.8
4	40.2	33.9	0.9	15.9	0.3	0.3	0.4	8.4
5 - deprived	41.3	33.2	0.8	14.7	0.4	0.2	0.2	9.3
subsite								
colon	42.0	41.9	0.2	5.5	0.2	0.4	0.3	9.5
rectosigmoid	39.4	35.7	0.8	18.1	0.1	0.2	0.5	5.3
rectum	33.5	21.0	2.0	34.7	0.8	<0.1	0.6	7.3
stage								
I	49.4	32.5	1.2	13.0	0.4	<0.1	0.1	3.3
II	45.5	35.0	0.9	12.9	0.3	0.1	0.2	5.0
III	33.3	36.0	0.7	17.8	0.4	0.4	0.6	10.9
IV	23.7	31.7	0.4	16.1	0.7	0.6	1.1	25.7
comorbidity								
none	42.7	38.4	0.9	17.3	0.1	<0.1	<0.1	0.5
1	38.1	30.4	0.4	7.1	1.7	0.8	2.0	19.6
2	11.9	9.4	0.1	1.1	3.2	2.3	3.4	68.7
3+	3.0	2.5	<0.1	0.5	1.9	2.1	1.8	88.2

Table 7.7: Odds ratio for treatment with: surgery only; surgery and chemotherapy; and surgery and chemoradiotherapy (reference = any other treatment not under evaluation), by clinical and demographic variables (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

	surgery only					surgery and chemotherapy					surgery and radiochemotherapy					no treatment				
		Odds ratio*					Odds ratio*					Odds ratio*					Odds ratio*			
			95% CI		p-value			95% CI		p-value			95% CI		p-value			95% CI		p-value
	%		lower	upper		%		lower	upper		%		lower	upper		%		lower	upper	
overall	39.2					35.1	-				15.3	-				8.5	-			
sex																				
men	35.6	1.00	-	-	<0.001	36.9	1.00	-	-	0.04	18.3	1.00	-	-	0.04	7.3	1.00	-	-	0.07
women	43.8	1.22	1.11	1.34		32.8	0.88	0.80	0.96		11.6	0.81	0.73	0.90		10.0	1.37	0.98	1.91	
age																				
15 to 44	21.1	1.00	-	-		43.3	1.00	-	-		28.2	1.00	-	-		5.2	1.00	-	-	
45 to 54	18.7	1.20	0.80	1.80		46.0	1.11	0.82	1.51		29.1	0.73	0.54	0.99		3.6	0.87	0.25	3.06	
55 to 64	24.2	1.94	1.33	2.82	<0.001	44.1	0.96	0.73	1.28	0.02	24.3	0.57	0.43	0.75		5.2	0.71	0.23	2.23	0.11
65 to 74	35.0	3.14	2.17	4.54		40.3	0.81	0.61	1.07		16.7	0.38	0.29	0.51		6.0	0.79	0.26	2.43	
75 to 84	51.8	6.94	4.79	10.06		27.7	0.47	0.35	0.62		8.3	0.18	0.13	0.24		10.7	1.03	0.33	3.15	
85 to 99	61.4	15.84	10.59	23.68		14.4	0.24	0.17	0.33		2.8	0.04	0.02	0.07	0.01	20.3	1.22	0.37	4.00	
deprivation																				
1 - affluent	36.6	1.00	-	-		37.3	1.00	-	-		16.0	1.00	-	-		7.5	1.00	-	-	
2	36.7	0.97	0.83	1.13	fitted	37.8	1.05	0.90	1.22	fitted deprivation	15.5	1.01	0.85	1.21	fitted	8.1	1.12	0.65	1.92	fitted deprivation
3	39.6	1.05	0.90	1.23	deprivation	34.6	0.94	0.80	1.09	gap=0.96	15.5	1.10	0.92	1.30	deprivation	8.8	0.99	0.58	1.70	gap=0.96
4	40.2	1.06	0.91	1.23	gap=1.06	33.9	0.92	0.79	1.06	p-value=0.02	15.9	1.11	0.94	1.32	gap=0.99	8.4	0.83	0.47	1.45	p-value=0.44
5 - deprived	41.3	1.25	1.08	1.44	p-value=0.002	33.2	0.87	0.76	1.00		14.7	0.93	0.79	1.09	p-value=0.02	9.3	0.92	0.57	1.48	
subsite																				
colon	42.0	1.00	-	-		41.9	1.00	-	-		5.5	1.00	-	-		9.5	1.00	-	-	
rectosigmoid	39.4	0.92	0.79	1.08	<0.001	35.7	0.60	0.51	0.71	0.02	18.1	3.65	3.07	4.35		5.3	0.69	0.37	1.30	0.02
rectum	33.5	0.67	0.60	0.75		21.0	0.27	0.24	0.31		34.7	10.94	9.73	12.30	0.10	7.3	0.60	0.40	0.92	
stage																				
I	49.4	1.00	-	-		32.5	1.00	-	-		13.0	1.00	-	-		3.3	1.00	-	-	
II	45.5	0.74	0.64	0.86	<0.001	35.0	0.97	0.83	1.13	0.04	12.9	1.69	1.42	2.01		5.0	0.86	0.50	1.47	0.003
III	33.3	0.48	0.41	0.55		36.0	1.14	0.98	1.32		17.8	2.80	2.37	3.32		10.9	0.63	0.37	1.09	
IV	23.7	0.41	0.31	0.55		31.7	0.99	0.75	1.31		16.1	2.61	1.91	3.58	0.06	25.7	5.17	2.72	9.83	
comorbidity																				
none	42.7	1.00	-	-		38.4	1.00	-	-		17.3	1.00	-	-		0.5	1.00	-	-	
1	38.1	0.77	0.60	0.99	<0.001	30.4	0.80	0.62	1.04	0.04	7.1	0.49	0.33	0.72		19.6	16.17	9.82	26.60	<0.001
2	11.9	0.31	0.22	0.44		9.4	0.29	0.20	0.41		1.1	0.09	0.04	0.19		68.7	113.59	76.28	169.14	
3+	3.0	0.10	0.05	0.21		2.5	0.11	0.05	0.25		0.5	0.05	0.01	0.26	0.04	88.2	302.95	176.78	519.14	

* adjusted for all factors in the table

Type of surgery

The specific type of surgery received can have a huge influence on a patient's survival, risk of recurrence, and probability of a colostomy, but operation type is also influenced by prognostic factors, such as stage and comorbidity. Whilst patients with early and advanced stage were equally likely to have surgery (known or imputed) there are stage-specific differences in the surgical options. Specific operation type was not included in the imputation model because of the large number of specific operation types and overlapping operation code definitions (e.g. excision of colon NOS, excision of transverse colon). Univariate analysis of specific operation type was evaluated but could not include imputed data, such as complete stage.

There were very few significant socioeconomic trends in specific operation type because of the small numbers for most specific operation types (Table 7.8). Deprived patients were less likely to have a surgery than affluent patients (no surgery: 15.7% and 19.6%, respectively) and were more likely to have operations associated with emergency treatment or non-curative treatment (e.g. Hartman's). For colon cancer surgery, affluent patients were significantly more likely than deprived patients to have an excision of the left hemicolon, sigmoid colon or colon (unspecified). For rectal cancer surgery, affluent patients were significantly more likely to have anterior resection than deprived patients. Deprived patients were less likely to have abdominoperineal excision for rectal cancer or Hartman's procedure (although neither was significant). A substantial minority of patients (16.2%) had colorectal surgery that was not recorded as an excision, but this was consistent across socioeconomic groups. Deprived patients were more likely to have no surgery recorded than affluent patients (15.7% and 19.6%). The higher proportion of missing data for deprived patients compared to affluent may suggest that some of the socioeconomic variations are because of missing surgery information. This could be further investigated if specific surgery information were available (e.g. emergency, intent, complications). Information on chemotherapy adherence and prevision prior to treatment may also help to elucidate the socioeconomic variations in treatment type.

Table 7.8: Distribution of surgical type (%) by socioeconomic status (original data): colorectal cancer patients diagnosed 1997-2004, North West of England

								All	
		OPCS-4	1 - affluent	2	3	4	5 - deprived	No.	%
colon	Total excision of colon and rectum	H04	0.6	0.6	0.5	0.4	0.4	138	0.5
	Total excision of colon	H05	0.7	0.7	0.6	0.5	0.6	180	0.6
	Extended excision of right hemicolon	H06	3.4	3.7	3.5	3.7	3.2	1,029	3.5
	Excision of right hemicolon	H07	16.1	17.1	17.2	16.9	15.9	4,894	16.6
	Excision of transverse colon	H08	0.8	1.0	0.9	0.8	0.7	244	0.8
	Excision of left hemicolon	H09	4.9	5.5	5.0	4.4	4.1	1,384	4.7
	Excision of sigmoid colon	H10	8.1	7.8	7.6	6.7	7.4	2,211	7.5
	Excision of colon	H11	3.4	2.8	2.3	2.4	2.7	792	2.7
	Extirpation of lesion of colon	H12	0.6	0.6	0.7	0.5	0.6	182	0.6
rectal	Abdominoperineal excision	H33.1	6.0	5.9	6.7	6.9	6.4	1,888	6.4
	Anterior resection	H33.2-H33.4, H33.6	17.5	16.9	15.6	14.8	14.6	4,639	15.7
	Hartmans	H33.5	5.7	5.6	5.8	7.0	7.6	1,920	6.5
	Other surgery		16.7	15.3	15.5	16.7	16.4	4,776	16.2
	None	-	15.7	16.9	18.4	18.6	19.6	5,343	18.1

Hospital and surgeon volume

There were moderate socioeconomic variations in the proportion of patients having operations at each level of hospital and surgeon volume. Deprived patients were more likely to have surgery at a high-volume or very high-volume hospital, but to have their surgery conducted by a low-volume surgeon (Table 7.9). In the absence of individual measures of hospital and surgical quality, surgical volume may provide an indication of the quality of peri-operative care and surgical expertise. Complex, curative and planned surgeries may also be completed by higher volume surgeons and hospitals. For rectal cancer patients, anterior resection and abdominoperineal resection were positively associated with both high-volume surgeon and high-volume hospitals, and inversely associated with Hartman's procedure (Appendix 7.1 and 7.2) There were no clear trends for colon cancer patients. Operations other than excisions were very common for low-volume hospitals. These trends clearly point towards differential surgery types but the lack of specificity of coding and missing data (both for treatment and prognostic factors) makes further interpretations difficult. For example, a large proportion of private patients were recorded as not receiving excisions (other non-curative surgery) but this was probably due to non-specific surgery codes. Most of the surgery information for private patients treated during 1997 to 2004 was obtained from pathology reports, rather than directly from private hospitals. In most cases it is therefore possible to determine if a patient had surgery but not the surgical procedure.

Surgeon and hospital volume were positively correlated, although even at high-volume hospitals a substantial proportion of patients were treated by low-volume surgeons (Table 7.10). This initially seems counter-intuitive but the majority of the very high-and high-volume hospitals in the North West are teaching hospitals, with trainee surgeons in these hospitals likely to have lower volumes. In the later years (after 2003) most of the hospitals designated to specialise in colorectal cancer surgery were teaching hospitals. Surgeon and hospital volume undoubtedly influence the specific surgery type a patient received, but this could not be assessed directly because of small numbers (as described previously). If surgeon and hospital volume effectively measure the quality of treatment, compliance with clinical guidance and provision of adjuvant therapy, then we would expect each of these to be positively associated with increasing hospital and surgeon volume. Even after adjustment for clinical and demographic factors higher-hospital volume and surgeon volume were positively associated with a higher odds of patients receiving of adjuvant therapy, or compliant treatment (Table 7.11 and 7.13).

Table 7.9: Distribution (%) of hospital and surgeon volume (colorectal surgeries per year) by socioeconomic status (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

		1 - affluent	2	3	4	5 - deprived	All
Hospital volume							
very high	(over 150)	24.8	27.9	26.3	25.1	26.6	**26.2**
high	(100 to 149)	31.4	34.1	37.5	36.2	36.7	**35.4**
moderate	(50 to 99)	23.0	18.6	19.0	20.7	17.9	**19.6**
low	(less than 50)	5.3	5.9	4.8	6.2	6.8	**5.9**
Private		5.8	3.5	2.0	1.3	0.9	**2.4**
none		9.7	10.1	10.5	10.5	11.2	**10.5**
Surgeon volume							
very high	(60 and over)	5.0	3.1	2.5	2.7	1.9	**2.9**
high	(40 to 59)	12.9	16.3	14.9	15.0	16.0	**15.7**
moderate	(20 to 39)	33.3	33.3	33.8	33.2	31.2	**32.7**
low	(less than 20)	35.3	37.1	38.1	38.7	39.8	**38.2**
none		10.0	10.2	10.8	10.5	11.1	**10.6**

Table 7.10: Distribution (%) of surgeon volume by hospital volume (colorectal surgeries per year) for surgical patients only (after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

surgeon volume		Hospital volume				
		very high (more than 150)	high (100 to 149)	moderate (50 to 99)	low (less than 50)	private (private)
very high	(60 and over)	4.1	3.2	3.6	2.0	3.3
high	(40 to 59)	26.0	16.3	9.9	12.5	17.9
moderate	(20 to 39)	32.0	39.7	37.4	35.1	34.2
low	(less than 20)	37.9	40.8	49.2	50.3	44.6

The proportion of patients receiving surgery and adjuvant therapy (either chemotherapy or chemoradiotherapy) was positively associated with hospital and surgeon volume (Table 7.11). Conversely, the proportion of patients receiving only surgery increased with decreasing hospital and surgeon volume and was highest for private patients (78.3%). Private patients were least likely to receive adjuvant therapy, although this may be mainly attributed to their case-mix and very good prognosis, including earlier stage at diagnosis. Hospital volume was more strongly associated with treatment regime than surgeon volume.

Increasing deprivation was still associated with an increase in treatment with surgery only, and less in surgery and chemotherapy, even after adjusting for hospital volume. Adjustment for hospital volume actually increased the inequality in treatment for surgery only, and surgery with chemoradiotherapy, possibly because of socioeconomic variations in hospital volume and the inclusion of private hospitals (Table 7.7). Deprived patients and patients treated privately were both most likely to receive surgery only. The good prognosis and case-mix for private patients suggested they were generally treated curatively were as deprived patients receiving surgery alone were treated curatively and palliatively.

Treatment regimes as a whole appear to be influenced by both hospital and surgeon volume, presumably because more experience or skill and adherence to guidance is associated with high-volume hospitals and high-volume surgeons. The consistent pattern could be attributed to centralisation of services, access to multidisciplinary expertise & oncology services and a better knowledge of and adherence to the most recent clinical guidance.

Table 7.11: Odds ratio for and distribution (%) of treatment with: surgery only; surgery and chemotherapy; and surgery and chemoradiotherapy (reference = any other treatment not under evaluation), by socioeconomic status, hospital and surgeon volume (colorectal surgeries per year) (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

		surgery only*					surgery and chemotherapy*					surgery and chemoradiotherapy*				
			odds ratio			p-value		odds ratio			p-value		odds ratio			p-value
				95% CI				95% CI					95% CI			
		%		lower	upper		%		lower	upper		%		lower	upper	
Hospital volume																
very high	(over 150)	32.8	1.00	-	-		49.2	1.00	-	-		17.2	1.00	-	-	
high	(100 to 149)	42.1	1.65	1.47	1.85		40.4	0.69	0.62	0.76		16.9	0.96	0.86	1.07	
moderate	(50 to 99)	48.5	2.23	1.95	2.56	<0.001	31.2	0.46	0.41	0.52	<0.001	19.2	1.11	0.97	1.26	<0.001
low	(less than 50)	66.0	4.39	3.51	5.48		18.1	0.24	0.19	0.30		13.8	0.88	0.70	1.10	
Private		78.3	13.40	9.47	18.96		10.3	0.10	0.07	0.16		8.8	0.35	0.24	0.53	
Surgeon volume																
very high	(60 and over)	45.4	1.00	-	-		29.2	1.00	-	-		24.0	1.00	-	-	
high	(40 to 59)	39.7	1.30	0.96	1.77	0.03	42.7	0.94	0.72	1.23	0.2	16.7	0.82	0.62	1.07	<0.001
moderate	(20 to 39)	41.5	1.20	0.89	1.62		38.1	0.85	0.65	1.11		19.5	1.06	0.81	1.37	
low	(less than 20)	46.9	1.44	1.07	1.94		37.4	0.91	0.70	1.19		14.8	0.73	0.56	0.95	
deprivation																
1 - affluent		36.6	1.00	-	-		37.3	1.00	-	-		16.0				
2		36.7	1.07	0.91	1.26		37.8	0.97	0.84	1.13		15.5	0.96	0.82	1.12	
3		39.6	1.19	1.01	1.41	<0.001	34.6	0.84	0.72	0.98	<0.001	15.5	1.05	0.90	1.23	0.82
4		40.2	1.16	0.99	1.36		33.9	0.84	0.72	0.98		15.9	1.06	0.91	1.24	
5 - deprived		41.3	1.41	1.21	1.64		33.2	0.76	0.66	0.88		14.7	0.94	0.81	1.08	

*adjusted for all variables in the table and age, sex, stage and comorbidity,

†Odds ratio could not be estimated due to small numbers

Compliance with guidance

Treatment regimes were assigned by stage at diagnosis based on the National Institute for Clinical Excellence guidance published in 1997, and up-dated in 2004.[8] A simple stage-specific estimate of compliance was generated, using the imputed treatment categories of surgery, chemotherapy, and radiotherapy. Treatment for stage IV colon and rectal cancer is generally non-curative and any treatment combination could be clinically appropriate; it was excluded from further analysis. This estimate of adherence with clinical guidance is an alternative method of assessing treatment receipt and quality, rather than a 'true' estimate of adherence to guidelines. Compliance in accordance with guidance was higher for colon cancer (72.5%) than for rectal cancer (64.6%) (Table 7.12). Treatment in accordance with clinical guidance was high for stage I and II but poor for stage III cancers, both for colon cancer and rectal cancer.

Table 7.12: Proportion of patients (%) treated in accordance with clinical guidance by subsite and stage (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

Stage	Treatment regime recommended by current guidance	Patients treated in accordance with guidance (%)
	Colon	
I	Surgery only	58.7
II	Surgery only or surgery and chemotherapy	96.0
III	Surgery and chemotherapy	57.6
IV	any combination except radiotherapy (will depend on patients diagnosis and overall health)	99.1
	Rectal and rectosigmoid†	
I	Surgery only	67.0
II	Surgery only or surgery and chemoradiotherapy	97.4
III	Surgery only or surgery and chemoradiotherapy	40.8
IV	any combination (will depend on patients diagnosis and overall health)	100.0

†Total mesorectal excision should be used for tumours in early stage but this does not have a specific code in OPCS-4 therefore any surgery was used in imputation and analysis

Compliance with guidelines measured in this way, was generally similar for both colon and rectal cancers (Table 7.13). Increasing deprivation was associated with lower compliance for colon cancer (deprived odds ratio 0.72), but there was no socioeconomic difference in rectal cancer.

Increasing age, deprivation and comorbidity were correlated with much lower compliance, even after adjustment, however this could be because of lower levels of adjuvant therapy identified earlier.

Rectal cancer surgery can require more specialist training, especially for total mesorectal excision (TME). It is therefore unsurprising that the patterns of treatment compliance for each hospital volume and surgeon volume were different for colon and rectal cancer patients. Rectal cancer patients treated at moderate- to low-volume hospitals had the highest proportion of patients treated in accordance with guidance but there was no difference after adjustment (Table 7.13). High surgeon volume for rectal cancer was associated with compliance but ideally information on anterior resection or TME would be used to assess compliance further. For colon cancer, increasing hospital and surgeon volume were associated with higher levels of treatment in accordance with guidance, even after adjustment. Private hospitals had the lowest adherence to guidance possibly because of the case-mix of patients treated privately. Surgeon volume had little impact on treatment compliance with guidance for colon cancer patients, decreasing from 83% for high-volume surgeons to 79% for low-volume surgeons.

Despite the limitations of this analysis it is still useful to see a general trend for higher compliance with higher volume hospital and higher surgeon volume. However, hospital and surgeon volume did not explain socioeconomic variations in treatment that was given in accordance with clinical guidance and warrants further investigation.

Table 7.13: Odds ratio for treatment in accordance with clinical guidance (reference = compliance) by clinical, demographic and treatment factors for colon and rectal cancer, excluding stage IV (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

	colon*			rectal and rectosigmoidal*		
		95% CI			95% CI	
		lower	upper		lower	upper
sex						
men	1.00	-	-	1.00	-	-
women	0.84	0.71	0.99	0.89	0.75	1.07
age						
15 to 44	1.00	-	-	1.00	-	-
45 to 54	0.93	0.46	1.87	0.67	0.37	1.21
55 to 64	0.61	0.33	1.14	0.55	0.32	0.96
65 to 74	0.43	0.24	0.80	0.43	0.25	0.75
75 to 84	0.20	0.11	0.36	0.28	0.16	0.48
85 to 99	0.09	0.05	0.18	0.18	0.09	0.36
deprivation						
1 - affluent	1.00	-	-	1.00	-	-
2	0.96	0.72	1.29	0.97	0.73	1.30
3	0.86	0.64	1.14	1.01	0.75	1.36
4	0.88	0.66	1.16	1.06	0.80	1.41
5 - deprived	0.72	0.56	0.93	0.95	0.73	1.24
comorbidity						
none	1.00	-	-	1.00	-	-
1	0.60	0.39	0.93	0.42	0.21	0.81
2	0.21	0.11	0.41	0.29	0.11	0.81
3+	0.26	0.06	1.21	0.26	0.02	3.88
Hospital volume						
very high (over 150)	1.00	-	-	1.00	-	-
high (100 to 149)	0.69	0.57	0.85	1.01	0.83	1.23
moderate (50 to 99)	0.60	0.48	0.76	1.40	1.11	1.76
low (less than 50)	0.61	0.38	0.97	1.43	0.95	2.16
Private	0.66	0.25	1.78	0.79	0.44	1.41
Surgeon volume						
very high (over 60)	1.00	-	-	1.00	-	-
high (40 to 60)	0.80	0.43	1.49	0.69	0.42	1.11
moderate (20 to 40)	0.77	0.42	1.42	0.92	0.58	1.48
low (less than 20)	0.68	0.38	1.25	0.86	0.53	1.38

* adjusted for sex, age, stage, deprivation and comorbidity

Summary

Inequalities in access to treatment may partially explain socioeconomic inequalities in survival. Deprived patients were less likely than affluent patients to have adjuvant therapy and more likely to receive their surgery from low-volume surgeons. Deprived rectal cancer patients were more likely to receive surgery types associated with poor outcomes (Hartman's procedure) and less likely to receive anterior resection. A broad

measure of whether treatment was given in accordance with guidance further identified some variations by socioeconomic group and this actually widened after adjustment for hospital and surgeon volume. Imputation managed missing stage, treatment and comorbidity data enabling analysis without large proportions of data missing, but required some grouping of information resulting in a loss of some specificity. For example, surgery was categorised into the occurrence or non-occurrence, rather than the specific type and quality measures (e.g. TME, emergency, curative, complications). It is always preferable to have full information without missing data, which could explain some of the socioeconomic variations.

Overall, deprived patients received lower levels of adjuvant therapy and may have received less than optimal surgical type and/or surgical quality than affluent patients. The apparent socioeconomic variations in access to treatment are a concern. They may not be the only cause of socioeconomic variations in survival, however if, survival for any given treatment is similar in all socioeconomic groups. The relationship between socioeconomic status, treatment and survival will be evaluated in the next chapter.

Appendix 7.1: Distribution (%) of surgery type by hospital volume (colorectal surgeries per year) for surgical patients only (unimputed data): colorectal cancer patients diagnosed 1997-2004, North West of England

		very high (more than 150)	high (100 to 149)	moderate (50 to 99)	low (less than 50)	private (private)	Total
	Total excision of colon and rectum	0.7	0.7	0.5	0.3	0.4	0.6
Colon	Total excision of colon	0.7	0.8	0.6	0.8	1.0	0.7
Colon	Extended excision of right hemicolon	4.5	4.3	3.8	4.9	3.3	4.1
Colon	Excision of right hemicolon	20.1	20.2	20.4	22.4	17.9	19.6
Colon	Excision of transverse colon	0.8	1.1	0.9	1.1	1.6	1.0
Colon	Excision of left hemicolon	5.8	5.7	5.6	5.4	5.2	5.8
Colon	Excision of sigmoid colon	10.1	8.6	8.8	8.6	9.7	9.2
Colon	Excision of colon	2.8	3.0	3.2	4.0	14.6	2.7
Colon	Extirpation of lesion of colon	0.8	0.6	0.5	2.2	2.6	0.4
Rectal	Abdominoperineal excision	8.5	7.8	7.9	4.2	3.3	8.6
Rectal	Anterior resection	7.5	7.7	7.9	3.8	2.6	8.3
Rectal	Hartman's	8.5	8.4	8.1	7.0	1.9	8.1
	Other non-curative surgery	29.2	31.2	31.8	35.3	35.9	30.8
		100.0	100.0	100.0	100.0	100.0	100.0

Appendix 7.2: Distribution (%) of surgery type by surgeon volume (colorectal surgeries per year) for surgical patients only (unimputed data): colorectal cancer patients diagnosed 1997-2004, North West of England

		very high (more 60)	high (40 to 59)	moderate (40 to 19)	low (less than 20)	Total
	Total excision of colon and rectum	1.3	0.8	0.8	0.3	0.6
Colon	Total excision of colon	1.0	0.8	0.7	0.8	0.7
Colon	Extended excision of right hemicolon	2.2	3.7	3.7	4.9	4.1
Colon	Excision of right hemicolon	18.8	19.3	18.8	20.6	19.6
Colon	Excision of transverse colon	1.2	0.7	0.9	1.2	1.0
Colon	Excision of left hemicolon	6.8	4.8	6.5	5.5	5.8
Colon	Excision of sigmoid colon	11.4	9.3	8.9	9.2	9.2
Colon	Excision of colon	2.1	2.9	2.4	3.0	2.7
Colon	Extirpation of lesion of colon	0.7	0.5	0.4	0.4	0.4
Rectal	Abdominoperineal excision	10.4	10.1	10.5	6.3	8.6
Rectal	Anterior resection	7.0	8.8	9.8	6.7	8.3
Rectal	Hartman's	5.9	7.9	7.2	9.3	8.1
	Other non-curative surgery	31.2	30.5	29.6	32.0	30.8
		100.0	100.0	100.0	100.0	100.0

(1) Morris E, Quirke P, Thomas JD, Fairley L, Cottier B, Forman D. Unacceptable variation in abdominoperineal excision rates for rectal cancer: time to intervene? *Gut.* 2008; 12:1690-1697.

(2) Wrigley H, Roderick P, George S, Smith J, Mullee M, Goddard J. Inequalities in survival from colorectal cancer: a comparison of the impact of deprivation, treatment and host factors on observed and cause specific survival. *Journal of Epidemiology and Community Health.* 2005; 57:301-309.

(3) Parry JM, Collins S, Mathers J, Scott NA, Woodman CBJ. Influence of volume of work on the outcome of treatment for patients with colorectal cancer. *British Journal of Surgery.* 1999; 86:475-481.

(4) Porter G, Soskolne C, Yakimets W, Newman S. Surgeon-related factors and outcome in rectal cancer. *Annals of Surgery.* 1998; 227:157-167.

(5) NYCRIS. *Cancer treatment policies & their effects on survival; colorectal.* Leeds: NYCRIS, 2000.

(6) Morris E, Haward RA, Gilthorpe MS, Craigs C, Forman D. The impact of the Calman-Hine report on the process and outcomes of care for Yorkshire colorectal cancer patients. *British Journal of Cancer.* 2006; 95:979-985.

(7) Haward RA. The Calman-Hine report: a personal retrospective on the UK's first comprehensive policy on cancer services. *Lancet Oncology.* 2006; 7:336-346.

(8) Department of Health. *Improving outcomes in colorectal cancer: the manual.* London: Department of Health, 1997.

(9) Association of Coloproctology of Great Britain and Ireland. *Guidelines for the management of colorectal cancer.* London: The Royal College of Surgeons of England, 2001.

Chapter 8

Are there socioeconomic differences in survival when deprived and affluent patients receive equivalent treatment?

Overview

Surgery, either alone or in combination with chemotherapy and/or radiotherapy, is the only curative treatment for colorectal cancer. Surgical outcomes have improved during the 1990s and 2000s because of improvements in post-operative care, the introduction of surgical techniques (e.g. total mesorectal excision and laparoscopic surgery), centralisation of services, and the increased use of neoadjuvant chemotherapy.[1,2] Regional variations in treatment in accordance with guidelines, surgeon factors (e.g. high-volume or specialist) and centralisation of treatment (e.g. high-volume or specialist centres) have been proposed as possible causes of the variations in survival.[3] However, the relationship of guidance, hospital volume and surgeon volume on inequalities is not known. Associations between treatment, clinical and demographic factors could explain socioeconomic inequalities in colorectal cancer survival. Yet it remains unclear if patients from deprived and affluent backgrounds have similar survival from the same treatment, after adjusting for clinically and demographically relevant factors.

Aims

The previous chapter highlighted socioeconomic variations in type and quality of treatment, particularly lower levels of adjuvant therapy among deprived patients. This chapter will report the analyses of inequalities in survival for specific treatment regimes for colorectal cancer patients, after adjusting for relevant clinical and demographic factors. Post-operative mortality will also be evaluated because it has a substantial impact on survival at one and five years and is strongly influenced by other factors, such as comorbidity. The influence of hospital and surgeon volume on survival will be analysed with adjustment for variations in case-mix. The impact of a broad measure of adherence to clinical guidance on the socioeconomic gap in survival will be assessed. Finally, socioeconomic variations will be evaluated after adjustment for treatment type, hospital and surgeon volume and case-mix to determine if socioeconomic inequalities in survival persist.

The analysis presented in this chapter will mainly be based on data after imputation, unless otherwise specified.

Treatment regimes

Socioeconomic inequalities in survival for each treatment regime persisted, even after adjustment for age, stage and comorbidity. For each treatment regime, socioeconomic inequality in survival at one year after diagnosis and was consistent across treatments (EHR 1.30 to 1.33), and generally higher, than for five year conditional survival (EHR 1.13 to 1.28) (Table 8.1). For example, the survival inequalities for patients treated with surgery and chemotherapy or with, surgery and chemoradiotherapy narrowed by about half after the first year of diagnosis (EHR at one year 1.33 and 1.32, five year conditional 1.16 and 1.13). Inequalities in survival decreased very little for patients treated with surgery only and no treatment between one year after diagnosis and five year conditional survival. The excess hazard ratio could not be analysed for surgery and radiotherapy, radiotherapy alone, chemotherapy alone and chemoradiotherapy alone because of the small number of patients by socioeconomic groups. These summary measures of treatment regime capture the overall trends but lack the specificity to determine if variations in the quality of treatment, particularly surgery explain these inequalities in survival.

Table 8.1: Excess hazard ratio of death at one year after diagnosis and at five years conditional on survival to one year, by treatment regime and socioeconomic status, adjusted for age, stage and comorbidity (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

	1 - affluent	2	3	4	5 - deprived	Linear coefficient of deprivation gap†	
One year							
Treatment							
surgery only	1.00	1.06	1.13	1.30	1.32	1.31	*
surgery and chemotherapy	1.00	0.95	1.12	1.20	1.31	1.33	*
surgery and radiotherapy‡	-					1.30	
surgery and radiochemotherapy	1.00	1.01	1.28	1.14	1.38	1.32	*
radiotherapy only	-					-	
chemotherapy only	-					-	
chemoradiotherapy only	-					-	
no treatment	1.00	1.30	1.27	1.38	1.47	1.32	*
Five year survival conditional on surviving the first year							
Treatment							
surgery only	1.00	1.03	1.13	1.36	1.36	1.28	*
surgery and chemotherapy	1.00	1.00	1.07	1.15	1.28	1.16	
surgery and radiotherapy	1.00	-					
surgery and chemoradiotherapy	1.00	1.01	1.04	1.10	1.17	1.13	
radiotherapy only	1.00	-				-	
chemotherapy only	1.00	-				-	
chemoradiotherapy only	1.00	-				-	
no treatment	1.00	1.27	1.27	1.42	1.55	1.26	

It was not possible to calculate estimates for surgery and radiotherapy, radiotherapy only, chemotherapy only, or chemoradiotherapy because of small numbers in these groups.

* p-value <0.05

† Regression for linear change in EHR between successive socioeconomic groups (estimated by multiplying the linear coefficient by 4 to obtain entire deprivation gap).

‡ Adjusted for age and stage

Surgery, either alone or in combination with radiotherapy and/or chemotherapy, is the only curative treatment for colorectal cancer. Most colorectal patients had surgery (90.5%). Further analysis will focus on inequalities in survival after surgical treatment, including the influence of hospital volume and surgeon volume. The annual number of colorectal cancer operations per year at the hospital and surgeon level will be evaluated as a measure of surgical quality (or expertise). Type and quality of surgery are different for colon cancer and rectal (including rectosigmoid), therefore socioeconomic variations in survival and surgery will be evaluated separately for each subsite.

Post-operative mortality

Post-operative mortality, or mortality within 30 days of surgery, was higher in deprived than affluent colorectal cancer patients. The risk of death for deprived patients compared to affluent fell from 1.35 to 1.22 after adjustment for age, stage, comorbidity, hospital volume and surgeon volume (Table 8.2). Post-operative mortality in colon cancer patients was almost double the post-operative mortality in rectal cancer patients (9.6%, 5.0%). Inequalities in post-operative mortality were wider for colon cancer and post-operative mortality was substantially higher for each socioeconomic group than rectal cancer. For example, 8.4% of affluent colon cancer patients died post-operatively compared to 11.0% of deprived patients (OR 1.24). For rectal cancer patients, only 4.3% of affluent patient died post-operatively increasing to 5.6% of deprived patients (OR 1.18). The disparities between socioeconomic groups and by subsite were not explained by differences in stage and comorbidity but may be partially attributable to differences in the type of operation received. The type of surgery a patient receives will be influenced by patient factors such as cancer subsite, and whether they presented with comorbidity or with advanced stage. Patients treated by higher volume surgeons have lower post-operative mortality, even after adjustment for these factors, but this may be partially because a higher proportion of patients received adjuvant therapy and planned surgery. Post-operative mortality was also influenced by the volume of colorectal cancer operations conducted by a hospital, but there was little variation between hospitals conducting a very-high (over 150 surgeries per year), high-volume (100 to 149 surgeries per year) and moderate-volume (50 to 99 surgeries per year). Higher post-operative mortality occurred for hospitals conducting a low-volume of surgeries per year (less than 50) (OR colon: 1.10, rectal: 1.28). Those patients treated in private hospitals had very low post-operative mortality (colon 3.8%, rectal 4.1%) because treatment at a private hospital was associated with better prognostic factors. In contrast, patients who had surgery at low-volume hospital may have been more likely to have presented as emergencies. Furthermore, complex surgery conducted by higher-volume surgeons or higher-volume hospitals would be expected to result in lower post-operative mortality than similar surgery conducted by low-volume surgeons, but the influence of this on socioeconomic inequalities in one-year and five-year survival conditional on surviving the first year is less clear.

Post-operative mortality decreased by about 30% between 1997 and 2004, even after adjusting for deprivation, stage and other factors (Table 8.2). This may provide a quantitative description of the positive impact of improvements in peri-operative care and the introduction of new surgical techniques, such as laproscopic surgery. Laproscopic surgery decreases the risk of infection and leakage and has lower post-operative mortality than open surgery.[4-7] The impact on longer term survival is yet to be quantified. but is expected to prove higher with laproscopic than open surgery.

There were very few socioeconomic trends in post-operative mortality for each type of surgery due to the small numbers (Table 8.3). Each type of operation is specifically for either colon or rectal cancer and will be discussed separately.

Colon

For colon cancer patients, post-operative mortality increased with increasing levels of age, deprivation and stage. There were substantial inequalities in post-operative mortality for colon cancer patients, with 11.0% of deprived patients dying post-operatively compared to 8.4% of affluent patients. The inequalities in post-operative mortality were higher for colon cancer than rectal cancer, and were not explained after adjustment. Age was most strongly associated with post-operative mortality, particularly for patients who were over age 75 at diagnosis who had a post-operative mortality of over 12%. Post-operative mortality was very high for colon cancer patients with a comorbidity level of 3 or more (36.3%), but was similar for patients with comorbidity levels of none to two (9.5% to 10.2%).

High post-operative mortality for colon cancer patients was mainly attributed to four surgical procedures: total excision of the colon (15.0%); extended right hemicolon (10.9%); transverse colon (12.3%); and sigmoid colon (12.9%) (Table 8.3). These procedures are generally more invasive. For each of these four surgery types post-operative mortality was higher in deprived than affluent patients. There was a consistent trend for higher post-operative mortality for most operations, however because of small numbers only excision of the right hemicolon and left hemicolon had significantly higher post-operative mortality.

The proportion of colon cancer patients dying post-operatively was similar for very high-, high- and moderate-volume hospitals (9.2% to 10.2%). Post-operative mortality was higher

for colon cancer patients who had surgery at low-volume hospitals (11.5%), even after adjustment for clinical and demographic factors (Table 8.2). Private hospitals had very low levels of post-operative mortality probably because all surgeries were elective. Higher surgeon volume was significantly associated with better post-operative mortality for colon cancer patients, even after adjustment for stage. Differences in post-operative mortality by surgeon volume may be partially attributed to case-mix, however this should be largely accounted for by adjusting for stage and comorbidity. For example, colon cancer patients presenting as an emergency with an obstruction may be more likely to be treated by a low-volume surgeon. Higher levels of adjuvant therapy associated with elective surgery would also be associated with higher volume surgeons, further influencing post operative mortality (see Table 7.11).

Rectal

Post-operative mortality for rectal cancer patients was less strongly associated with deprivation and stage compared to colon cancer. For example 5.6% of deprived rectal cancer patients died post-operatively compared to 4.3% of affluent (1.18), whereas 11.0% of deprived and 8.4% of affluent colon cancer patients died post-operatively (1.24), respectively. Surgical intent (curative, palliative, elective or emergency) may explain some of the differences between rectal and colon cancer but this information was not available for this study. Advanced stage was associated with a large post-operative mortality (8.8%, OR 3.6) for rectal cancer patients, although this may be partially explained by differences in procedure type (emergency, type of surgery). Post-operative mortality for rectal cancer patients increased with comorbidity but was accounted for after adjustment. Post-operative mortality for patients with a comorbidity level of 3 or more could not be estimated due to small numbers.

Most of the post-operative mortality for rectal cancer patients occurred following other (non-excision) surgeries (11.2%) (Table 8.3). Post-operative mortality for colon and rectal cancer patients was particularly high for Hartman's procedure (12.4%). Anterior resection and abdominoperineal excision for rectal cancer had very low post-operative mortality (3.8% and 1.7%, respectively). The very good post-operative outcomes for anterior resection and abdominoperineal resection may be attributed to both the curative intent of the surgery and case-mix.

Post-operative mortality for rectal cancer patients was similar for very high- to moderate-volume hospitals (4.5% to 5.2%) and private hospitals (4.1%). Similarly, post-operative mortality for rectal cancer patients was consistent for very high- to moderate-volume surgeons (3.6% to 3.7%). Rectal cancer patients who had surgery at a low-volume hospital (6.3%) or a low-volume surgeon (7.3%) had much higher post-operative mortality. The high post-operative mortality in low-volume hospitals and surgeons was associated with a higher proportion of patients having Hartman's procedure and lower proportion having received adjuvant therapy.

Table 8.2: Post-operative mortality: Distribution (%) of patients dying within 30 days of surgery and Odds ratio for death within 30 days of surgery by clinical and demographic factors (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

	colorectal (n=26,162)				colon (n=15,942)				rectal (n=10,220)			
		Odds ratio*				Odds ratio*				Odds ratio*		
	%		95% CI				95% CI				95% CI	
Total	7.8	-			9.6	-			5.0	-		
Sex												
Men	7.4	1.00	-	-	9.4	1.00	-	-	4.8	1.00	-	-
Women	8.4	0.91	0.88	0.94	9.9	0.91	0.88	0.95	5.3	0.89	0.84	0.95
Age												
15 to 44	0.8	1.00	-	-	1.1	1.00	-	-	0.4	1.00	-	-
45 to 54	2.5	3.37	2.56	4.45	2.9	2.76	2.03	3.77	2.1	5.59	2.96	10.59
55 to 64	4.0	5.55	4.26	7.24	5.3	5.49	4.10	7.36	2.4	6.20	3.31	11.61
65 to 74	6.3	8.88	6.83	11.54	7.9	8.51	6.37	11.37	3.9	10.72	5.75	20.02
75 to 84	10.8	16.11	12.39	20.94	12.4	14.73	11.03	19.66	7.8	22.38	12.00	41.74
85 to 99	18.3	30.68	23.57	39.92	21.6	29.04	21.71	38.84	11.8	37.74	20.19	70.58
Deprivation												
1 - affluent	6.8	1.00	-	-	8.4	1.00	-	-	4.3	1.00	-	-
2	6.2	0.84	0.80	0.89	7.4	0.81	0.76	0.86	4.3	0.93	0.84	1.04
3	7.9	1.05	1.00	1.10	9.9	1.09	1.02	1.15	4.8	0.96	0.86	1.06
4	8.4	1.11	1.06	1.17	10.4	1.13	1.07	1.20	5.2	1.07	0.97	1.18
5 - deprived	8.9	1.22	1.17	1.28	11.0	1.24	1.17	1.31	5.6	1.18	1.08	1.29
Diagnosis year												
1997	9.5	1.00	-	-	11.9	1.00	-	-	5.7	1.00	-	-
1998	9.3	1.00	0.95	1.06	11.4	0.98	0.92	1.04	6.2	1.05	0.94	1.17
1999	7.3	0.73	0.69	0.78	9.0	0.72	0.68	0.77	4.6	0.78	0.70	0.88
2000	7.8	0.82	0.77	0.86	9.6	0.80	0.75	0.85	5.1	0.88	0.78	0.98
2001	7.3	0.75	0.71	0.80	9.0	0.73	0.68	0.78	4.6	0.81	0.72	0.91
2002	6.7	0.69	0.65	0.74	8.0	0.66	0.61	0.70	4.7	0.82	0.73	0.92
2003	7.6	0.79	0.75	0.84	9.5	0.78	0.73	0.83	4.8	0.86	0.77	0.96
2004	6.7	0.71	0.66	0.75	8.5	0.70	0.65	0.75	4.1	0.74	0.66	0.84
Subsite												
colon	9.6	1.00	-	-	-	-	-	-	-	-	-	-
recotsigmoid	5.7	0.63	0.60	0.67	-	-	-	-	-	-	-	-
rectum	4.8	0.54	0.52	0.56	-	-	-	-	-	-	-	-
Stage												
I	3.5	1.00	-	-	4.1	1.00	-	-	2.9	1.00	-	-
II	6.5	1.61	1.50	1.72	7.8	1.82	1.66	1.98	4.3	1.38	1.24	1.53
III	9.7	2.76	2.58	2.94	12.0	3.20	2.94	3.50	6.0	2.16	1.96	2.39
IV	12.5	4.27	3.91	4.67	14.6	4.84	4.33	5.41	8.8	3.64	3.12	4.24
Comorbidity												
none	7.7	1.00	-	-	9.5	1.00	-	-	4.9	1.00	-	-
1	9.6	0.98	0.91	1.06	10.5	0.91	0.83	0.99	7.9	1.25	1.08	1.44
2	9.1	1.02	0.89	1.17	10.2	0.99	0.84	1.16	7.0	1.14	0.88	1.47
3 or more	10.8	2.33	1.89	2.86	36.3	4.16	3.29	5.26	-	-	-	-
Hospital volume												
very high (over 150)	8.0	1.00	-	-	10.2	1.00	-	-	4.8	1.00	-	-
high (100 to 149)	7.6	0.96	0.93	1.00	9.2	0.91	0.87	0.95	5.2	1.11	1.04	1.19
moderate (50 to 99)	7.7	0.91	0.87	0.95	9.8	0.91	0.87	0.96	4.5	0.88	0.81	0.96
low (less than 50)	9.8	1.15	1.08	1.22	11.5	1.10	1.03	1.18	6.3	1.28	1.13	1.44
Private	3.9	0.56	0.49	0.63	3.8	0.44	0.38	0.52	4.1	1.03	0.83	1.28
Surgeon volume												
very high (over 60)	5.5	1.00	-	-	6.7	1.00	-	-	3.8	1.00	-	-
high (40 to 60)	5.7	0.99	0.89	1.10	7.4	1.01	0.89	1.14	3.6	0.93	0.77	1.12
moderate (20 to 40)	6.3	1.09	0.98	1.20	8.3	1.15	1.02	1.29	3.7	0.93	0.78	1.11
low (less than 20)	10.2	1.61	1.46	1.78	11.6	1.57	1.40	1.77	7.3	1.76	1.48	2.10

*Adjusted for all variables in the table

87.6% of colon cancer patients and 90.1% of rectal cancer patients recieved surgery

Table 8.3: Post-operative mortality: Number and percentage of (%) of patients dying within 30 days of surgery for each type of surgery and socioeconomic group (original 'complete' data): colorectal cancer patients diagnosed 1997-2004, North West of England

		OPCS-4	Post-operative mortality No.	Post-operative mortality %	Affluent No.	Affluent %	Deprived No.	Deprived %	Absolute deprivation gap	
Colon	Total excision of colon and rectum	H04	5	3.6	2	7.1	2	5.6	-1.6	
	Total excision of colon	H05	27	15.0	4	12.5	11	21.6	9.1	
	Extended excision of right hemicolon	H06	112	10.9	15	9.0	29	10.5	1.4	
	Excision of right hemicolon	H07	425	8.7	58	7.5	132	9.6	2.2	*
	Excision of transverse colon	H08	30	12.3	5	12.5	8	12.7	0.2	
	Excision of left hemicolon	H09	102	7.4	15	6.4	37	10.5	4.1	*
	Excision of sigmoid colon	H10	150	6.8	21	5.3	41	6.5	1.2	
	Excision of colon	H11	102	12.9	18	10.9	36	15.7	4.7	
	Extirpation of lesion of colon	H12	10	5.7	2	7.1	4	8.0	0.9	
Rectal	Abdominoperineal excision	H33.1	71	3.8	8	2.8	19	3.4	0.7	
	Anterior resection	H33.2-H33.4, H33.6	77	1.7	9	1.1	21	1.7	0.6	
	Hartman's	H33.5	238	12.4	39	14.1	83	12.7	-1.4	
	Other non-curative surgery		533	11.16	80	9.9	167	11.8	1.9	
	Total		1,882	8.6	276	8.2	590	10.0	1.8	

* p-value <0.05

Hospital and surgeon volume

Patients receiving surgery at high-, moderate- or low-volume hospitals patients had similar survival at one year (73.3% to 74.2%) with survival positively associated with hospital volume by five years after diagnosis (52.3% to 53.2%) (Figure 8.1).

Patients receiving surgery at a private hospital had substantially higher relative survival at one (93.3%) and five years after diagnosis (69.5%) than other patients, but treated only 2.4% of patients. Non-surgical patients had the poorest survival and largest excess mortality in the first months after diagnosis but there was still a substantial minority alive at five years after diagnosis (one year 32.7%; five years; 21.0%).

Surgeon volume was also positively associated with survival at five years, although up to five years after diagnosis moderate-, high- and very high-volume surgeons had similar survival (Figure 8.2). Low-volume surgeons had consistently lower relative survival at all follow-up times (one year: 67%, five years: 47.0%). Five-year relative survival was 61.3% (95% CI 60.0, 62.6) for very high-volume surgeons (over 60), 59.2% for high-volume and 56.9% for moderate-volume surgeons. Non-surgical patients had the lowest relative survival at all follow-up periods.

Survival variations by hospital and surgeon volume are mostly explained by case-mix, which will in turn impact on surgical options and adjuvant therapy. The type of surgery received for rectal cancer varied widely by surgeon volume and hospital volume, but there was little variation for colon cancer. As identified earlier, high-volume surgeons and high-volume hospitals were generally associated with curative surgery with better outcomes (see Appendix 7.1 and 7.2). However, socioeconomic differences in colorectal cancer survival by surgeon volume or hospital volume still exist even after adjustment for factors that might be associated with surgery type (comorbidity, stage and other factor).

Figure 8.1: Relative survival up to five years after diagnosis by hospital volume (colorectal surgeries per year) (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

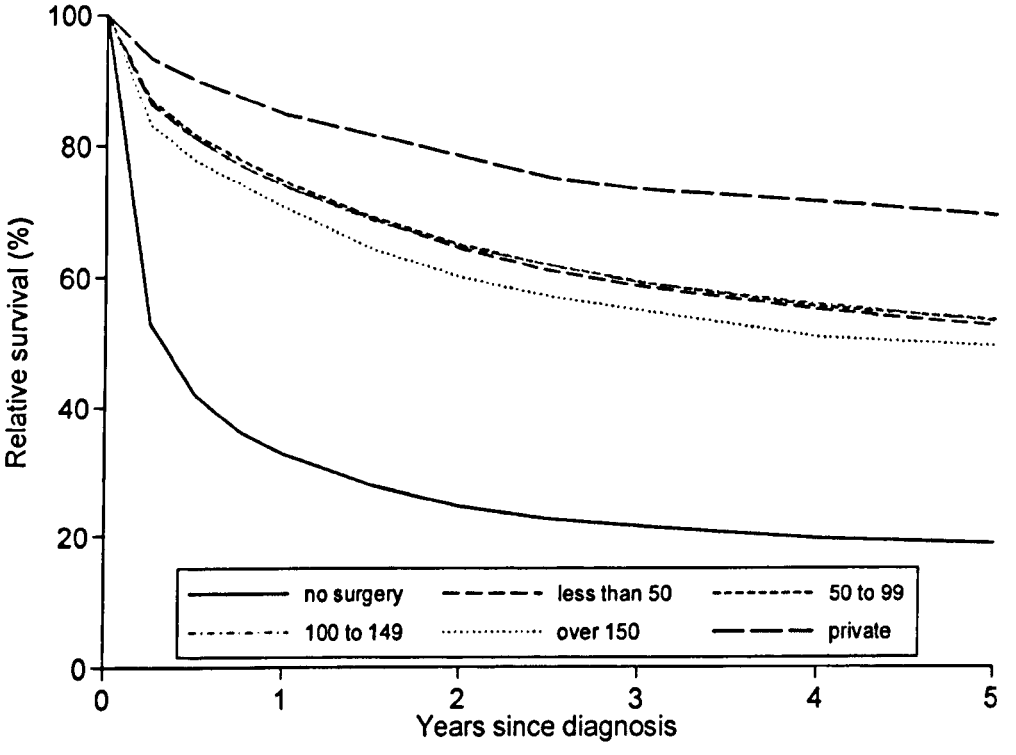
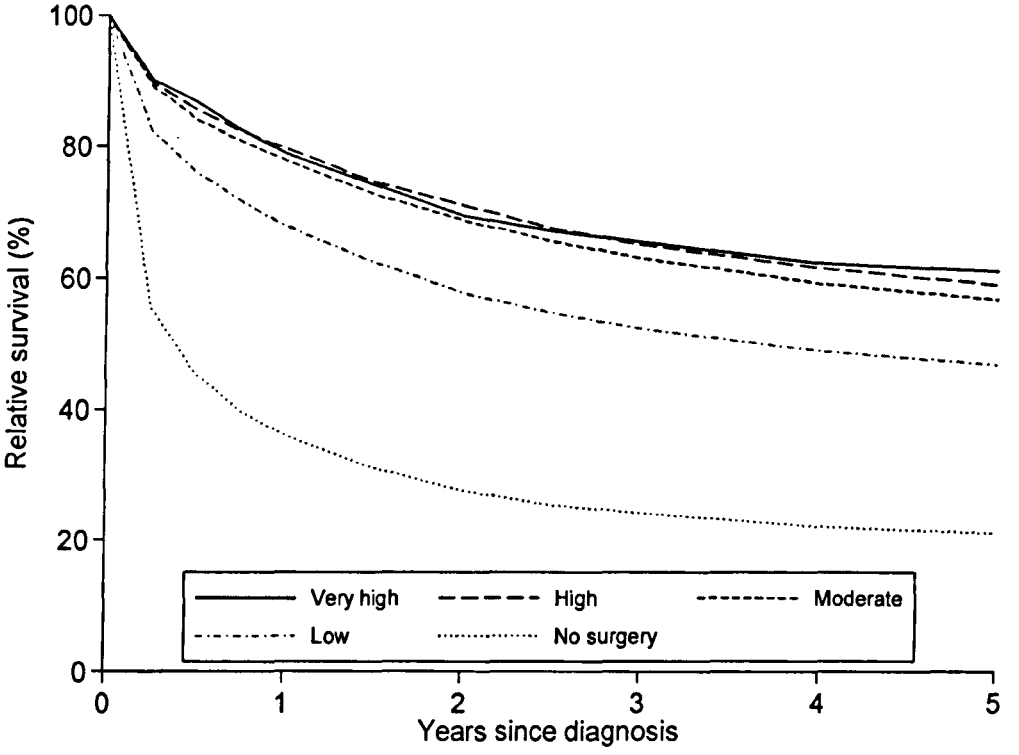


Figure 8.2: Relative survival up to five years after diagnosis by surgeon volume (colorectal surgeries per year) (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England



Socioeconomic inequalities in survival were observed for all hospital and surgeon volumes at one year after diagnosis, but they were slightly narrower for five year survival conditional on surviving the first year, even after adjustment (Table 8.4). In the first year after diagnosis, survival inequalities were very similar for all hospital volumes, ranging from an excess hazard ratio of death of 1.26 in high-volume to 1.41 for moderate volume. For patients who survived the first year after diagnosis, a substantial deprivation gap in survival remained for patients treated at high- and moderate-volume hospitals but none occurred for very high- or low-volume hospitals. For private hospitals the number of operations (and patients) was too low, particularly in the most deprived, to estimate the deprivation gap.

There was no consistent pattern in the socioeconomic inequalities in survival by surgeon volume for both one year or five year survival conditional on surviving the first year. Deprived patients treated by very high-volume surgeons had an extremely high excess mortality (EHR 1.70) which was narrowed after the first year following diagnosis.

Moderate and low-volume surgeons had similar levels of inequality at one year after diagnosis; survival inequalities persisted only for low-volume surgeons for five year survival conditional on surviving the first year.

Table 8.4: Excess hazard ratio of death for one-year survival and five year conditional survival by hospital and surgeon volume (colorectal surgeries per year), adjusted for age, stage and comorbidity (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

		1 - affluent	2	3	4	5 - deprived	Linear coefficient of deprivation gap†	
One year								
Hospital volume								
very high	(over 150)	1.00	0.97	1.27	1.21	1.32	1.31	*
high	(100 to 149)	1.00	0.95	1.02	1.19	1.21	1.26	*
moderate	(50 to 99)	1.00	1.06	1.17	1.19	1.50	1.41	*
low	(less than 50)	1.00	1.11	0.96	1.30	1.39	1.28	
no surgery		1.00	1.25	1.27	1.26	1.43	1.30	*
Surgeon volume								
very high	(over 60)	1.00	1.25	1.22	1.63	1.92	1.70	*
high	(40 to 60)	1.00	0.89	1.13	1.13	1.06	1.13	
moderate	(20 to 39)	1.00	0.96	1.12	1.25	1.40	1.38	*
low	(less than 20)	1.00	1.03	1.12	1.19	1.32	1.30	*
Five year survival conditional on surviving the first year								
Hospital volume								
very high	(over 150)	1.00	1.01	0.94	0.99	0.92	0.92	
high	(100 to 149)	1.00	0.93	1.00	1.16	1.16	1.22	*
moderate	(50 to 99)	1.00	1.04	1.07	1.19	1.40	1.35	*
low	(less than 50)	1.00	1.18	1.25	1.02	1.17	1.07	
no surgery		1.00	1.05	1.07	1.20	1.28	1.25	
Surgeon volume								
very high	(over 60)	1.00	1.01	1.49	1.48	1.51	1.52	
high	(40 to 60)	1.00	0.91	0.83	1.00	1.00	0.80	
moderate	(20 to 39)	1.00	1.10	1.11	1.09	1.12	1.08	
low	(less than 20)	1.00	0.99	1.00	1.22	1.27	1.28	*

It was not possible to calculate estimates patients receiving colorectal surgery at private hospitals because of small numbers in these groups.

* p-value < 0.05,

† Regression for linear change in EHR between successive socioeconomic groups (estimated by multiplying the linear coefficient by 4 to obtain entire deprivation gap),

Private hospitals

Patients receiving private surgery had significantly higher survival even after adjustment for age, stage, subsite and comorbidity. Higher survival for private patients was largely due

to these patients being generally younger, diagnosed at an earlier stage, and with lower levels of comorbidity than colorectal cancer patients in the North West. Most private patients received surgery alone (79%), compared with 39.2% for patients treated at an NHS hospital. After adjustment for age, stage, subsite and comorbidity, survival was significantly better in private patients.

Private surgical patients were also more affluent than the North West colorectal cancer population, with 65% from the two most affluent groups compared to 33% of colorectal cancer patients in NW. The specific type of surgery received by private patients was difficult to assess because of lack of access to case notes, but based on their earlier stage, and low levels of comorbidity, the surgical procedures were likely to have been curative. In short, private patients are a tiny but highly selected sub-set of patients, with a lower risk of death.

Guidance

Treatment in accordance with clinical guidelines for colon and rectal cancer patients was associated with better survival at one and five years. Patients with very advanced disease (stage IV) were excluded from these analyses (consistent with analysis in chapter 7) because most treatment regimes could be considered clinically appropriate, although inclusion of patients diagnosed in stage IV produced very similar trends. Compliance was associated with a much higher survival at five years (unadjusted EHR: 0.41 95% CI 0.38, 0.44, data not shown). The protective effect of compliance was still significant after adjustment for sex, age, subsite, stage, comorbidity, diagnosis year and deprivation (EHR: 0.66, 95% CI 0.61, 0.70, data not shown).

Inequalities in survival were observed for both compliant and non-compliant treatment (Table 8.5). Survival inequalities for colon and rectal cancer were higher in the first year after diagnosis than at five years conditional on surviving the first year after diagnosis, a pattern similar to that observed for treatment and other variables (stage, comorbidity) (see chapter 6). For rectal cancer patients treated in compliance with guidance the inequality in survival narrowed after the first year of diagnosis (from 1.41 to 1.22) but widened for non-compliance (from 1.23 to 1.33). After the first year of diagnosis, there were no inequalities in compliant or non-compliant treatment for colon cancer. Variations in treatment

(emergency, complications, compliance) may explain the pattern of inequalities in survival for compliant treatment because of the overlap between treatment regimes and compliance. The consistent pattern of lower survival in deprived patients, for each treatment regime and compliant treatment raises the question of whether fuller details of treatment type (complications, chemotherapy toxicity and adherence) and quality could help to explain these disparities further.

Table 8.5: Excess hazard ratio of death for treatment in accordance with clinical guidance for one-year survival and conditional survival at five years, adjusted for age and stage, excluding stage IV (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

	1 - affluent	2	3	4	5 - deprived	Linear coefficient of deprivation gap†	
One year							
Colon							
Compliance	1.00	1.00	1.16	1.26	1.42	1.41	*
Non-compliance	1.00	1.15	1.16	1.33	1.39	1.33	*
Rectal (and rectosigmoid)							
Compliance	1.00	1.00	1.29	1.30	1.44	1.41	*
Non-compliance	1.00	0.96	1.09	1.11	1.23	1.23	*
Five year survival conditional on surviving the first year							
Colon							
Compliance	1.00	1.10	0.99	1.07	1.11	1.11	
Non-compliance	1.00	1.03	0.91	1.21	1.15	1.19	
Rectal (and rectosigmoid)							
Compliance	1.00	0.98	1.02	1.19	1.19	1.22	*
Non-compliance	1.00	1.12	1.36	1.35	1.40	1.33	*

Patients in stage IV were not included (see text)

† Regression for linear change in EHR between successive socioeconomic groups (estimated by multiplying the linear coefficient by 4 to obtain entire deprivation gap),

* p-value < 0.05,

The relationship between deprivation, clinical guidance, hospital and surgeon volume

In the first year after diagnosis, there was a substantial deprivation gap in survival for colon cancer (39%) and rectal cancer (29%), which could not be explained after accounting for differences in hospital volume or clinical and demographic factors (Table 8.6). Socioeconomic inequalities were minimal for five year survival conditional on surviving the first year after diagnosis. Compliance was not adjusted for in analysis of deprivation because it is on the causal pathway to survival (Figure 9.2).

The basic estimate of whether treatment was in accordance with clinical guidance was associated with a markedly reduced excess hazard of death for both colon and rectal cancer (EHR: 0.82 and 0.81, respectively). Treatment in accordance with guidance did not, however explain the deprivation gap in survival for either colon or rectal cancer (colon: 1.36, rectal 1.28, data not shown). Excess hazard of death was not adjusted for treatment regime because it was closely associated with survival and is on the causal pathway (Figure 9.1).

Colon cancer

For colon cancer patients, increasing deprivation was positively associated with the excess hazard of death in the first year after diagnosis but only slightly associated after the first year. After adjustment for age, stage and comorbidity hospital and surgeon volume had very little impact on moderating the excess hazard of death by socioeconomic group. There was a significant trend towards higher survival with increasing hospital volume, although there was no significant excess mortality for patients receiving surgery at any hospital volume within the NHS. Similarly, the excess risk of death increased with decreasing surgeon volume but was significant only for low-volume surgeons. Survival was substantially higher for privately treated patients than patients in NHS hospitals.

Rectal cancer

Socioeconomic inequalities were narrower for one year and five year conditional survival for rectal cancer patients than colon cancer patients. The general pattern of excess mortality for each level of surgeon and hospital was similar for both rectal cancer and colon cancer patients. However, rectal cancer patients had a slightly lower excess mortality than colon cancer patients at most hospital and surgeon volumes. For example rectal cancer patients who had surgery from a low-volume surgeon had an excess mortality of 1.33, compared to 1.43 for colon. Patients who did not have surgery had an excess mortality of 1.61, compared to 2.37 for colon). This moderation in the association between hospital volume in rectal cancer resulted in no significant association between hospital volume and excess mortality.

Table 8.6: Excess hazard of death by hospital and surgeon volume, treatment in accordance with guidance and socioeconomic status (data after imputation): colorectal cancer patients diagnosed 1997-2004, North West of England

	Colon						Rectal					
	First year			up to Five years after diagnosis†			First year			up to Five years after diagnosis†		
		95% CI			95% CI			95% CI			95% CI	
Hospital volume*												
more than 150	-			1.00	-	-	-			1.00	-	-
100 to 150				0.98	0.92	1.04				0.98	0.89	1.07
50 to 99				1.03	0.95	1.10				0.96	0.87	1.06
less than 50				1.12	0.98	1.27				1.14	0.96	1.36
private				0.70	0.57	0.87				0.71	0.53	0.95
none				1.77	1.50	2.09				1.35	1.09	1.69
Surgeon volume*												
more than 60	-			1.00	-	-	-			1.00	-	-
40 to 60				1.00	0.81	1.22				0.98	0.78	1.24
20 to 39				1.10	0.91	1.33				0.99	0.79	1.23
less than 20				1.43	1.18	1.73				1.33	1.06	1.66
none				2.37	1.85	3.03				1.61	1.32	2.13
Guidance*												
Non-compliance				1.00	-	-	-			1.00	-	-
Compliance				0.82	0.74	0.90				0.81	0.74	0.89
Deprivation‡												
1 - affluent	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
2	1.07	0.97	1.19	1.01	0.88	1.16	1.00	0.86	1.17	1.00	0.84	1.18
3	1.18	1.07	1.30	0.93	0.81	1.07	1.16	1.01	1.34	1.08	0.92	1.28
4	1.29	1.18	1.42	1.03	0.90	1.18	1.15	1.00	1.32	1.19	1.02	1.38
5 - deprived	1.39	1.27	1.52	1.08	0.95	1.22	1.29	1.14	1.47	1.18	1.02	1.37

* adjusted for age, stage, grade, comorbidity, deprivation and interaction between deprivation and time.

† Estimates for second to fifth year after diagnosis for deprivation,

‡ adjusted for hospital volume, surgeon volume, age, stage, comorbidity, and interactions between deprivation and time.

Summary

Even when deprived patients received the same treatment regime or surgery in a high-volume hospital or from a high-volume surgeon, they had lower one year and post-operative survival. Excess mortality was similar for patients treated at very high-, high- and moderate-volume surgeons and hospital volume but was significantly higher for low-volume surgeons and hospitals. Patients treated at private hospitals had significantly higher survival but they were younger, diagnosed at an earlier stage and had fewer comorbid conditions than colorectal cancer patients in the North West.

Provision of optimal treatment is the aim of clinical guidance, but even when deprived patients receive treatment in line with guidance colon and rectal cancer patients survival was still lower than affluent patients. The continued inequality in colorectal survival, even within a specific treatment regime or hospital/surgeon volume may be due to socioeconomic differences in treatment quality or other factors that could not be fully investigated in this data set. However, these inequalities in survival, combined with the lower levels of adjuvant therapy, highlights issues of equality, a particular concern in a National Health Service based on equal access to optimal treatment for all patients.[8]

Reference List

(1) McArdle CS, McKee RF, Finlay IG, Wotherspoon H, Hole DJ. Improvement in survival following surgery for colorectal cancer. *British Journal of Surgery.* 2005; 92:1013.

(2) Morris E, Haward RA, Gilthorpe MS, Craigs C, Forman D. The impact of the Calman-Hine report on the process and outcomes of care for Yorkshire colorectal cancer patients. *British Journal of Cancer.* 2006; 95:979-985.

(3) McCarthy M, Datta P, Khachatryan A, Coleman MP, Rachet B. Would compliance with cancer care standards improve survival for breast, colorectal and lung cancers? *Journal of Epidemiology and Community Health.* 2008; 62:650-654.

(4) Leroy J, Jamali F, Forbes L, Smith M, Rubino F, Mutter D, Marescaux J. Laproscopic total mesorectal excision (TME) for rectal cancer surgery: long-term outcomes. *Surgical Endoscopy.* 2004; 18:281-289.

(5) Sasaki A, Nitta H, Otsuka K, Takahara T, Nishizuka S, Wakabayashi G. Ten-year experience of totally laparoscopic liver resection in a single institution. *British Journal of Surgery.* 2009; 96:274-279.

(6) NG KH, NG DC, Cheung HY, Wong JC, Yau KK, Chung CC, Li MK. Laparoscopic resection for rectal cancers: lessons learned from 579 cases. *Annals of Surgery.* 2009; 249:82-86.

(7) Colon Cancer Laparoscopic or Open Resection Study Group, Buunen M, Veldkamp R, Hop WC, Kudry E, Jeekel J, Haglind E, Pahlman L, Cuesta MA, Msika S et al. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncology.* 2009; 10:44-52.

(8) Expert Advisory Group on Cancer. *A policy framework for commissioning cancer services: a report by the Expert Advisory Group on cancer to the Chief Medical Officers of England and Wales.* London: Department of Health, 1995.

Chapter 9

Discussion and conclusions

Overview

Wide socioeconomic inequalities in survival for colorectal cancer were found in the North West for patients diagnosed between 1997 and 2004, particularly in the first year after diagnosis. These inequalities were not explained by variations in stage, comorbidity or other clinical and demographic factors. Deprived patients, were less likely to receive adjuvant therapy and more likely to have had surgery, particularly surgery alone, than affluent patients. Deprived patients, were also less likely to receive curative surgery, particularly anterior resection for rectal cancer, and more likely to die within 30 days of colorectal cancer operation than affluent patients. Substantial inequalities in survival persisted even when deprived and affluent patients received similar treatment regimes. Determining the appropriate treatment regime involves many clinical factors, such as stage and comorbidity. However, even after adjusting for many of these factors, adjuvant therapy and survival remained lower for deprived patients. The inter-relationship between type and quality of treatment, clinical factors and demographic factors is complex (Figure 9.1). The main influences on treatment regime were taken into account (stage, comorbidity, age, surgeon volume and hospital volume), but they explained very little of the socioeconomic disparities in treatment. A large number of factors that are weakly associated with treatment and survival could not be evaluated in this study (lifestyle factors, biological differences, complications, adherence to treatment). However, it seems unlikely that any of these factors could explain the wide socioeconomic inequalities in treatment and survival that are reported here.

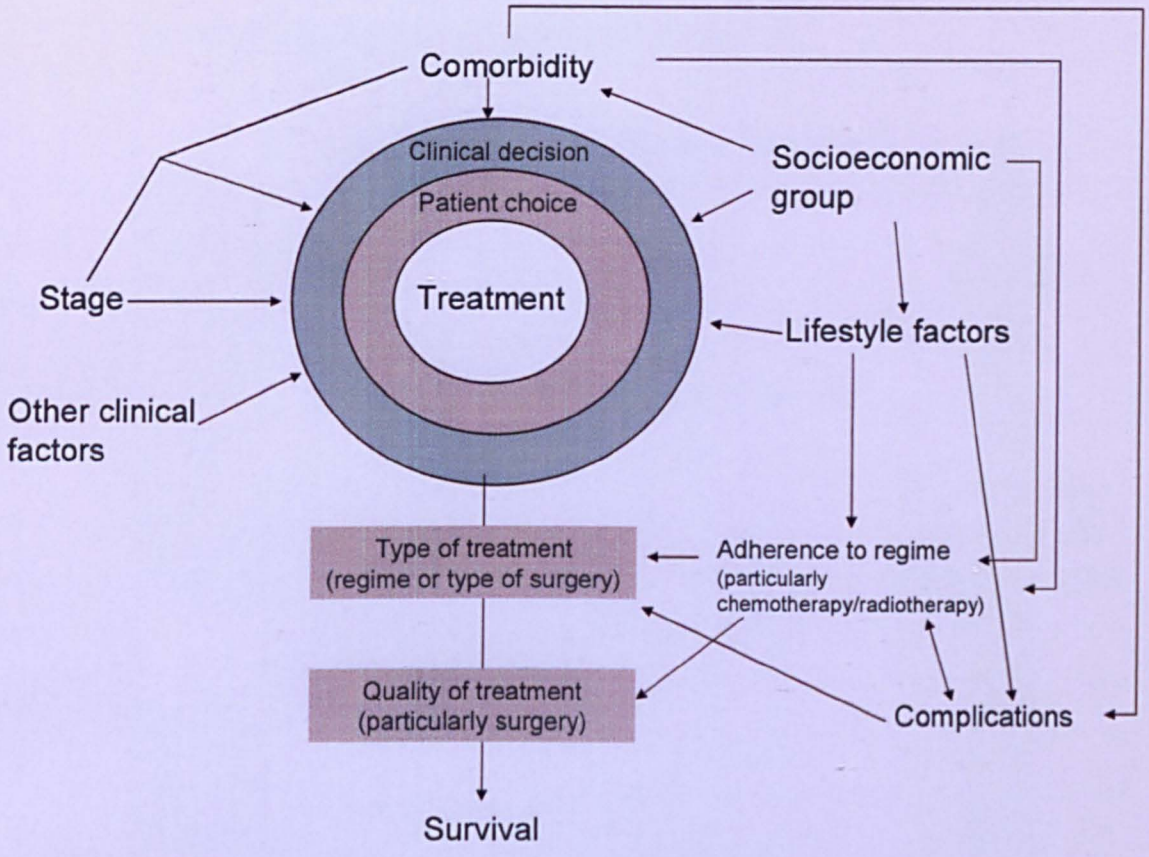
The National Health Service in the UK is founded on principles of equity, and persistent socioeconomic inequalities in treatment access and survival are therefore a source of concern. Inequalities in survival and access to treatment for colorectal cancer patients occurred in the North West region between 1997 and 2004 and given the higher take-up of colorectal screening in affluent populations may actually widen. Evidence-based strategies, to address socioeconomic inequalities in treatment access and to ensure consistent outcomes regardless of socioeconomic position are, likely to be the most effective way to address survival disparities.

Socioeconomic status

Socioeconomic inequalities in survival existed for up to five years after diagnosis, but the widest disparity was observed in the first year after diagnosis. Adjustment for clinical and demographic factors explained very little of this inequality in survival.

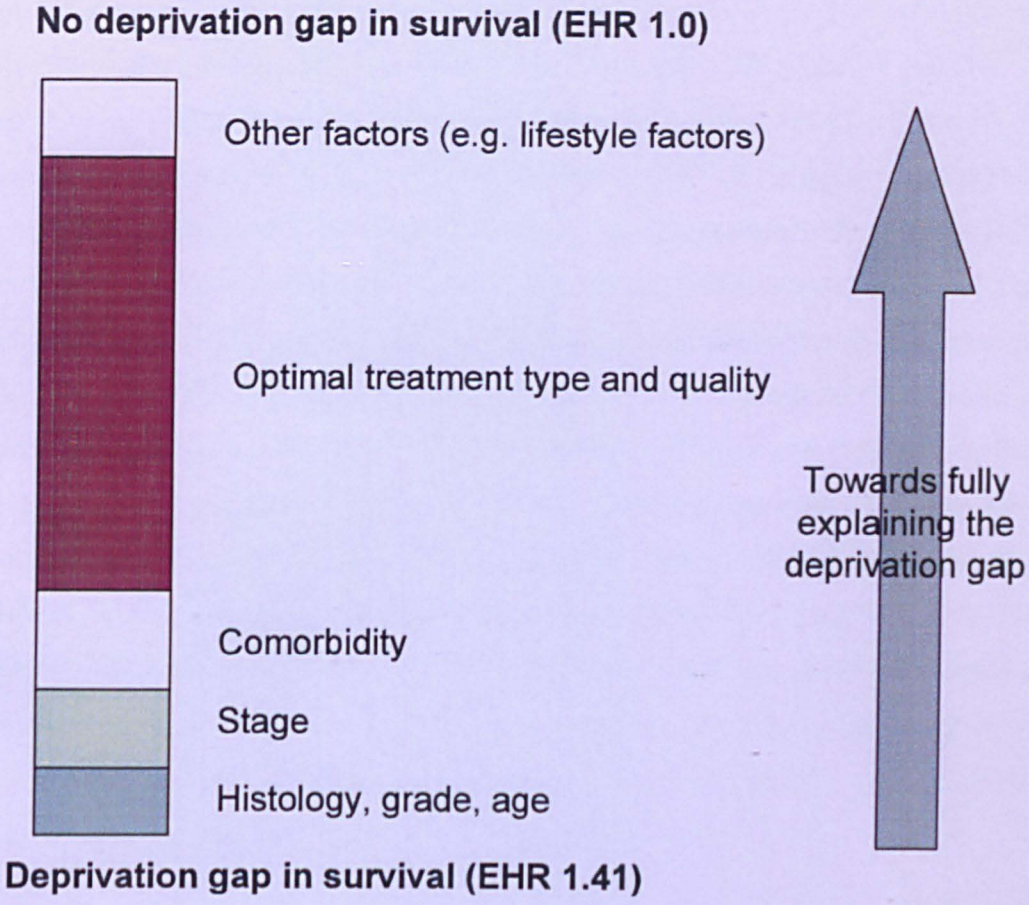
Survival for colon and rectal cancers improved substantially in England and Wales between 1986 and 1999, yet the socioeconomic inequalities continued to increase.[1] Whilst factors such as stage, comorbidity, age and treatment regime have the biggest impact on survival, survival is also influenced by other factors, either directly or through influences on the eligibility for and effectiveness of treatment. Figure 9.1 is a schematic diagram showing the likely direction of the influence of the complex inter-relationship of factors influencing socioeconomic inequality in both the type and quality of treatment and subsequent survival. Treatment is at the centre of this model, which is influenced directly by layers of clinical and patient decisions. Clinical decisions are strongly influenced by quantifiable clinical factors (e.g. stage, comorbidity) but these clinical factors may also explain most of the socioeconomic variations in survival. Each of these quantifiable factors will be discussed separately. Clinical decisions may also be influenced by 'softer' factors, such as the patient's health knowledge, lifestyle and characteristics. These 'softer' influences incorporate the personal interactions, lifestyle factors and characteristics that are difficult to quantify but may well influence decisions, both consciously and subconsciously.

Figure 9.1: Influences on inequality in colorectal cancer treatment and survival (based on an original concept from Polite *et al.* 2006, see Figure 2.1)



A recurring explanation for health inequalities is that affluent patients play a more active role in treatment decisions and that as a result they are more likely to receive optimal treatment and have higher survival than deprived patients.[2] A sociological theory, known as the 'Fundamental cause theory', takes this a step further, suggesting that people of higher socioeconomic status have a 'broad range of flexible and multi-purpose resources that can be used to the advantage of their health, including knowledge, money, power and social connections'.[3] The theory suggests that affluent patients may have better psychological and physical resources to request and obtain optimal treatment, or to obtain optimal treatment privately. Furthermore, affluent patients may be better able to remove potential barriers to treatment (e.g. transportation, financial, time off work) and to gain access to other resources (e.g. private medical advice, home support, external information on treatment options), than deprived patients. Individually, these may have little impact, but the combined influences on treatment, and ultimately survival could be substantial (Figure 9.2).

Figure 9.2: Proposed hierarchy of factors contributing to the inequalities in survival in the UK



In a universal-access health system that aims to provide equal access to treatment to all members of society, it seems counterintuitive that inequalities in outcome should persist. However, when risk factors that cause health inequalities are removed, social disparities in health have remained.[4] Rather than suggesting that reducing health disparities is futile, the fundamental cause theory suggests an alternative approach to ensure equitable access, by focusing on redressing inequalities through overtly ensuring optimal treatment for all socioeconomic groups. Actively empowering deprived patients with health knowledge could further serve to remove barriers to optimal treatment (including adherence).

Stage

Advanced stage at diagnosis was strongly associated with lower survival, but it explained very little of the socioeconomic inequalities in survival. At each stage, deprived patients had lower survival than affluent patients, although there were no socioeconomic variations in stage at diagnosis. By contrast, other researchers propose that a higher proportion of deprived than affluent patients present at a more advanced

stage contributed substantially to the socioeconomic inequalities in both colon and rectal cancer survival.[2,5] The impact of stage on socioeconomic inequalities in survival has been difficult to quantify, because population-based colon and rectal cancer data are often missing data on stage at diagnosis for between 15% and 40% of patients.[6-11] Missing data on stage were associated with older age, lower levels or quality of treatment,[8] poor prognosis and lower socioeconomic status[12] for colorectal patients in this study, and in other studies of population-based cancer registry data. Variations in the case-mix of patients with missing data on stage could explain some of the deprivation gap. Without the 'true' stage at diagnosis, it is impossible to adjust for stage because 'ad hoc' methods for adjustment (e.g. exclusion of missing data, inclusion of cases with missing data as a separate category) would not fully adjust for stage. In this study, stage-specific socioeconomic inequalities in survival remained at one year after diagnosis and for five-year conditional survival. With the presence of stage-specific inequalities, it is unsurprising that adjustment for stage after imputation did not significantly narrow the deprivation gap in survival. The wide stage-specific inequalities in survival may be attributed to i) differential staging by socioeconomic groups ii) incomplete adjustment for other patient characteristics (e.g. comorbidity, patient choice) or iii) differential treatment, for which stage is the main predictor.

Earlier stage at presentation of affluent colorectal cancer patients who, therefore achieved longer survival ('lead time'), has been suggested as a possible explanation for survival inequalities.[2,13] Earlier stage at diagnosis has been seen in audit studies for affluent colorectal cancer patients,[14] but results from population-based studies have been inconsistent.[9,13,15] This discrepancy is unsurprising, given that case ascertainment for population-based cancer data is less biased[16] than audit studies, which are biased towards patients who are actively treated. Earlier presentation in affluent patients for other cancer types[9,17,18] may be due to higher symptom awareness, whilst the non-specific nature of colorectal cancer symptoms may make it less likely that affluent patients would present at an earlier stage. Deprived colorectal cancer patients were more likely to have missing data for stage in, this and other studies[8,12] which may explain the reported association between advanced stage and deprivation. The records of affluent patients were more likely to have complete staging information, thereby biasing the observed stage distribution toward an earlier stage at diagnosis, because patients with missing data for stage generally had more advanced disease. There do not appear

to be any population-based studies of survival for colorectal cancer with either data on stage for all patients or in which missing stage data have been adequately imputed.

Stage at diagnosis can be further sub-divide within stage (e.g. Stage IIA and IIB).[19] If these sub-divided stage varies systematically by socioeconomic status it could contribute to socioeconomic inequalities in survival, and this differences would not be accounted for by imputation. Subdivision of stage II and III (e.g. Stage II: B1, B2; Stage III: C1 C2) was only available for 22% of patients (n=6,450), therefore it was necessary to use the less specific stage groupings (I-IV). Heterogeneity within stage is therefore plausible, but it is unlikely to cause the large stage-specific socioeconomic differences in survival.

Accurate staging is clinically important to determine if adjuvant therapy should be provided. Specialist centres are more likely to accurately stage patients and provide adjuvant therapy to their patients.[20,21] Stage-specific clinical guidelines for colorectal cancer encourage the recording of high-quality stage data, but they may have also contributed to inter-hospital variations. In this study, high-volume hospitals and high-volume surgeons were more likely to stage patients fully. This probably reflects better recording systems, a greater familiarity with clinical guidance and higher proportions of patients given active treatment.

Ideally, stage should be obtained from pathology to ensure accuracy and comparability, but for non-surgical patients stage must be obtained from clinical assessment, or preferably by imaging (also known as clinical stage). The accuracy of stage improves with an increasing number of lymph nodes sampled[22] (usually >12) but this is dependent both on the surgeon excising the tumour by wide margins (to maximise the number of lymph nodes), and on the pathologist testing and recording a large number of lymph nodes for tumour-positive status. Clinical stage is unlikely to be recorded in routine electronic datasets that are not cancer-specific, such as HES, and therefore to be captured by cancer registries or other data organisations (e.g. NHS Information Centre). The metastatic status of cancer is diagnosed from imaging (e.g. CT) and is therefore also less likely to be recorded in the cancer registry. Further research to elucidate the variations in staging methods and completeness between socioeconomic status could clarify differences in 'true' stage and why stage data are less complete for deprived patients.

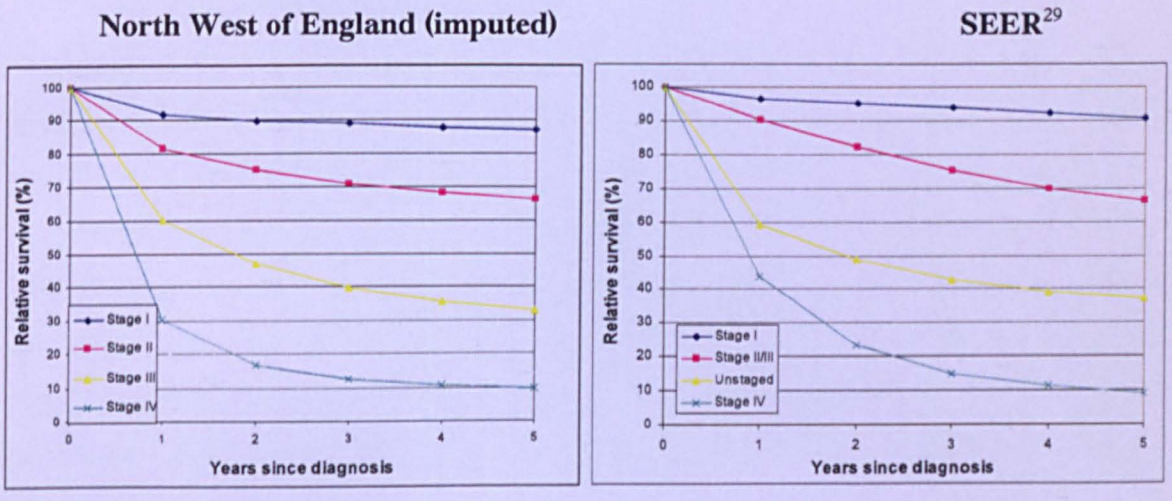
Survival for each stage at diagnosis decreased in the North West after imputation of missing data on stage. This is because patients with missing data on stage had a poorer prognosis, were generally older and had more comorbidity than patients whose stage was recorded. For example, patients with missing stage data and who were assigned to stage I after imputation of stage, had a poorer prognosis than those with stage I recorded in the original data. This reduced the overall relative survival estimate at five years for patients in stage I from 93.3% in the original data to 87.2% after imputation. This may be thought of as an example of the Will Rogers phenomenon, in which an undefined group, after assignment to specific categories, can reduce survival for all groups.[23,24] As comedian Will Rogers would say 'When the Okies left Oklahoma and moved to California, they raised the average intelligence of both states'.[23,24]

It is impossible to know the 'true' population-based distribution of stage for colorectal cancer patients. Multiple imputation was used to impute missing data, particularly stage, resulting in a pattern of stage-specific relative survival comparable with that of the Surveillance Epidemiology and End Result programme in the USA (1998 to 2002) (Figure 9.3). For example, five year relative survival was 90.5% for the US and 87.2% in the North West after imputation (Stage IV: 9.1% in US and 9.4% in NW). Colorectal cancer survival in the North West of England is generally below that of the USA, although lower stage-specific colorectal cancer survival in England, than the USA has been previously identified and mainly attributed to a lower proportion of patients receiving surgery.[25] The distribution of cases by stage, after imputation, was also consistent with other population-based studies in which colon cancer patients are mostly diagnosed in stage II and rectal cancer patients in stage III (Table 9.1).[8,25-28] There is wider variation in the distribution of stage I and IV between studies. Stage I generally accounts for between 4% and 14% of colorectal patients,[8,25-28] which was consistent with this study (11%).

Hospital-based audits generally found a higher proportion of patients with advanced disease, probably because patients had more thorough assessment for curative treatment. Additionally, patients with early-stage cancers may be treated at non-specialist centres where hospital-based audits rarely occur. In particular, one study found 27% of patients with stage IV, but this was a hospital audit of patients receiving adjuvant therapy and therefore biased as described above.[28] The proportion of patients in stage IV at 5% (2%

in original data) was lower in this study than other studies. This is attributed to the application of the standard exclusion used in survival analyses; to exclude patients without a date of diagnosis (death certificate only). 'Death certificate only' (DCO)[m] patients generally had a poor prognosis, most likely because of advanced stage. Death certificate only patients accounted for 2.8% of all patients, which would make the estimated proportion of patients diagnosed in advanced stage (7.8%) consistent with other population-based studies (ranging from 4% to 21%).[8,25-28] Additionally, population-based studies had lower proportions of advanced stage because when staging is done by imaging or from inadequate pathological specimens, stage tends to be underestimated.[26] This is more likely to occur in population-based data because they include patients who do not receive curative treatment. Despite the lower proportion of stage IV patients in this study, the stage-specific survival is consistent with other population-based studies.[8,29]

Figure 9.3: Stage-specific survival up to five years after diagnosis for the North West of England 1997 to 2004 and Survival and Epidemiology End Results (SEER), USA, 1998 to 2002



[m] Death Certificate Only (DCO) registration occurs when the only information about a patient is found on the death certificate.

Table 9.1: Distribution (%) of stage at diagnosis for selected studies of colorectal, colon and rectal cancer in population-based or large hospital-based audits.

		Stage				
		I	II	III	IV	unknown
Colorectal						
This study*	**North West of England, population-based, 1997-2004 (n=29,563)**					
	Original data	**7**	**25**	**26**	**2**	**40**
	After imputation	**11**	**38**	**47**	**5**	
Tilney *et al.* 2006	England-wide surgical audit (NBOCAP), 2005.	14	36	32	18	
Kelsal *et al. in press*	Melborne, Australia, nested cohort study (Melborne Collaborative cohort study) 1990-1994 (n=526)	23	28	28	17	3
Nur *et al.* 2008	England and Wales, Clinical trial of adjuvant radiotherapy and chemotherapy (5-FU), 1996-97 (n=2,481)	12	39	31	8	10
Brewster *et al.* 2001	Scotland, case-note audit, 1993 (n=2,778)	9	34	23	21	13
Munro *et al.* 2004	Dundee, Scotland, hospital-based audit, 1997-1999 (n=483)	4	25	43	27	
Ciccolallo *et al.* 2004	USA & Europe, but will present the UK data availible, 1990-91					
	Mersey and Cheshire region, case-note audit, (n=207)	11	29	23	23	14
	Thames region case-note audit, (n=176)	12	30	24	23	11
Colon						
Jestin *et al.* 2005	Uppsala region, Sweden, audit of rescected patients based on cancer registry data,1997-2002 (n=3,735)	12	42	31	15	1
Rectal						
Morris *et al.* 2008	England-wide population-based, 1998 to 2004 (n=31,223)	17	24	30	4	26

Comorbidity and lifestyle factors

Comorbidity in colorectal cancer patients was associated with poor survival. After adjustment, comorbidity explained very little of the deprivation gap in survival. The prevalence of comorbid conditions was higher in patients who were deprived, older and at an advanced stage, each of these being independently associated with poor survival. The severity and number of comorbid conditions was particularly associated with increasing age, both in this and other studies.[10,30-34] Comorbid conditions reduced clinical eligibility for certain treatments and increased the complexity of treatment, particularly surgery, and are consequently associated with lower survival[31] and shorter life expectancy after diagnosis.[35]

Increasing levels of comorbidity were associated with a higher excess hazard ratio of death in the first year after a colorectal cancer diagnosis, especially when comorbid conditions occurred with 18 to 6 months before colorectal cancer diagnosis. After adjustment for age, deprivation, stage and duration of follow-up, the excess hazard ratio at one year after diagnosis was slightly higher for a given level of the Charlson measure than the Ghali measure. The Charlson comorbidity measure identified more comorbid conditions and had a stronger association with the excess hazard ratio at one year, despite the comorbid conditions in Ghali being a subset of the Charlson. Additional

conditions, such as chronic pulmonary disease, liver disease, previous cancer, that are included in the Charlson measure improved its association with survival.

The use of administrative databases to derive the data for measures of comorbidity introduces many limitations and challenges, particularly relating to the lack of specific data (e.g. complication of cancer treatment), accuracy of clinical coding and system or coding changes over time. Although HES data quality and accuracy have been questioned, comparisons with audit data[36,37] have found they produce representative and comparable results for post-operative mortality following cardiac, bowel cancer or abdominal aortic aneurysm surgery, and surgical volume for bowel cancer. Some gaps in completeness remain, particularly at individual Trust level. For example, in some records only the acute care trust of treatment was recorded, rather than the specific hospital (e.g. Pennine acute trust, rather than one of the four specific hospitals within it). The prevalence of previous tumours and metastatic tumours in this research obtained from registry data was consistent with other studies,[10,34] whilst HES data overestimated, this possibly due to recording of suspected cancer (e.g. suspected stomach later determined to be colorectal). HES may be very good at recording illnesses that are contra-indicators for treatment. For example Ischemic Heart Disease is a contra-indicator for some chemotherapy treatments and was detected in 7% of colorectal cancer patients. Hospital administrative databases undoubtedly under-estimate the frequency of diseases which do not normally require hospital treatment, such as diabetes without complications. Alternatively, HES may not record when patients have other common chronic conditions, such as obesity. In this study, for example, the prevalence of obesity recorded in HES data was 0.4% in colorectal patients, compared with a population prevalence of 24% for men and 36% for women during 2003 in the North West of England.[38]

Co-occurrence of colorectal cancer with other conditions, such as heart disease, pulmonary disease and diabetes, is to be expected, because they share some environmental and lifestyle risk factors.[39] Cardiovascular disease, chronic obstructive pulmonary disease (COPD), hypertension, diabetes and one or more previous cancers have been consistently identified in other studies as the most frequent comorbid conditions among the colorectal cancer patients, regardless of the methods used in the study.[10,33-35,40] In particular, cardiovascular disease and COPD significantly affected survival.[32,34,35,40] The frequency of comorbidity observed in this study, was lower than

in many clinical studies, but it was consistent with other population-based studies.[10,28,30,32,34]

With the exception of diabetes and chronic obstructive pulmonary disease, the prevalence of specific comorbid conditions was similar, to a population-based study of comorbidity (using medicare claims) in colorectal cancer patients aged over 66 without missing data on stage (I-IV) and diagnosed in the USA between 1992-1996.[40] The prevalence of diabetes among the general population in England at 3.3%,[41] was comparable to the prevalence of 2.9% for colorectal patients in this study (diabetes with complications 2.7%; diabetes without complications 0.2%). In contrast, the US comorbidity study in colorectal cancer patients found the prevalence of diabetes with complications to be 6.4% in men and 5.4% in women (diabetes without complication 0.6% for both men and women) but this may be partially explained by the study selection criteria, which excluded patients under the age of 66, those with unusual histology and with missing data on stage. The prevalence of chronic obstructive pulmonary disease was estimated to be between 4% and 10% based on an international meta-analysis.[42] This range of COPD prevalence is consistent with the prevalence observed in the present study for colorectal cancer patients in North West of England (7.9%). It is unclear whether differences in risk factors or health systems might explain these differences. One hypothesis is that patients in the USA receive more thorough assessments and treatment, particularly in the case of those likely to require surgical procedures.[25]

There is increasing evidence that lifestyle choices may improve survival and decrease recurrence for cancer patients.[43-45] Studies of the influence of lifestyle choices on colorectal cancer have mainly focused on lifestyle choices and recurrence, although it may logically follow that lower recurrence rates are likely to improve survival. Whilst comorbidity was measured and adjusted for in the present study, data on lifestyle choices and general health were not available. Adverse lifestyle factors, such as smoking, obesity, poor diet and low levels of exercise[38] are all consistently more common in deprived communities. All of them are negative prognostic factors for diagnostic procedures, treatment options and survival; both through poorer general health and specific comorbid conditions. A high body mass index (BMI) has been associated with poorer prognosis after adjuvant therapy.[46] Low levels of exercise and a diet high in red meat and fat, and low in vegetables, have been associated with lower

survival for colon and colorectal cancers but not for rectal cancer.[47] Taken together the increased risk of poor diet, low levels of exercise and obesity put deprived patients at a further disadvantage, with deprived patients less likely to improve these factors after diagnosis.

In cancer patients, smoking significantly increases post-operative mortality, and the risk of complications.[48,49] Prevalence of smoking is higher among deprived socioeconomic groups and in manual occupations, although smoking has recently become less common in the these groups, particularly since the introduction of the smoking ban in England in 2008.[50] The higher smoking prevalence among deprived patients could substantially contribute to post-operative mortality and in turn influence inequalities at both one year (and possibly five years). It is unclear how much of the socioeconomic inequalities in post-operative mortality could be explained by variations in smoking. Quitting smoking, even after a cancer diagnosis, could well improve survival.

Tumour biology and genetics

There were no socioeconomic variations in the distribution of grade or histology at diagnosis. Patients diagnosed with a non-specific subsite or non-specific morphology had a poorer prognosis than others, while adenocarcimoma was associated with a better prognosis. Socioeconomic inequalities in survival occurred for both adenocarcinomas and mucinous and serous histological types (EHR at one year: 1.32, and 1.40, respectively), but socioeconomic inequalities in grade narrowed with increasing grade (EHR at one year: 1.37 to 1.32). A study of colorectal cancer survival differences in Europe and the USA found that adjustment for morphology partially explained variations in survival.[51] However, as in the present study of the North West of England, the European cancer registries had a significantly higher proportion of patients with unspecified subsite (10%) and morphology (15%) than the USA (North West of England: 13.9% and 11.6%, respectively). Higher proportions of patients with specific histology and subsite might be because of the higher proportion of colorectal patients receiving surgery in the US.[52] In order to detect the small differences in survival implied by variations in histology large scale studies scale studies such as these (Europe n=151,244; USA n=53,884) were required.

Biological differences in invasive breast cancer between socioeconomic groups have been recorded, such as lower oestrogen receptor status in deprived women,[53] but there

has been no evidence of biological differences for colorectal cancer. A number of inherited or acquired genetic abnormalities are associated with colorectal cancer in particular ethnic groups.[54,55] In order for these to affect socioeconomic survival the genetic abnormalities would need to influence survival and the ethnic group would also have to be strongly associated with socioeconomic status, both of which may occur. A recent study found that colorectal cancers in African Americans had higher levels of microsatellite instability.[56] There is some evidence that cancers with microsatellite instability are less likely to respond to fluorouracil-based chemotherapy.[57] There is still too little information on genetic abnormalities and survival to assess the magnitude of these genetic and ethnic relationships, although the impact on socioeconomic variations in survival is probably very small.

Access to treatment

Socioeconomic variations in treatment regime and the quality of surgery partially explain socioeconomic inequalities in survival. Deprived patients received less adjuvant chemotherapy and/or radiotherapy than affluent patients. Increasing deprivation was associated with surgical procedures that were conducted by less experienced surgeons (low-volume surgeons). Receipt of sub-optimal surgery was also associated with increasing deprivation; deprived patients were more likely to receive Hartman's procedure and less likely to receive anterior resection than affluent patients.

If different socioeconomic groups are diagnosed at the same stage and level of comorbidity, why do they receive different treatment? Factors related to the patient, the treating physician and the health service may each influence the treatment regime received by the patient. Even after adjusting for the major patient influences on treatment (age, stage, comorbidity, subsite), substantial socioeconomic differences in treatment remained. Patient factors may still explain some of the socioeconomic variation, but it is unlikely that they alone can explain the large magnitude of inequalities. Deprived patients may be more likely to have other factors making them less likely to take-up treatment or attend treatment appointments. Lower levels of education may decrease the ability to play an active role in treatment planning and increase apprehension. Additionally, incomplete or outdated knowledge of cancer prognosis would result in an expectation of a poor outcome. Despite treatment being free incidental costs (e.g. transportation, time off work) may influence receive radiotherapy and chemotherapy and/or adhere to the full regime. The fundamental cause

theory summarises the influence of patient factors on inequalities and highlights the greater ability affluent patients may have to obtain psychological and physical resources to request and obtain optimal treatment (see page 226). These factors are outside of the direct control of clinicians and health service control but would be expected to decrease the proportion of deprived patients receiving treatment.

Affluent patients may benefit from fewer comorbid conditions, thereby influencing the treatment, but even after adjusting for comorbidity there were still socioeconomic variations in treatment. The comorbidity measure may under-represent illness, particularly diseases that do not require hospital admission, but this under-estimation is not likely to be biased by socioeconomic status. Clinical treatment plans must take into account the whole person, including non-quantifiable factors. Even a small bias toward less than optimal treatment regimes for deprived patients based on the perceived presence of risk factors for outcome (e.g. poorer general health) may result in a substantial contribution to systematic socioeconomic differences in treatment.

Chemotherapy

Inequitable access to chemotherapy, known in the popular media as the 'postcode lottery' is a controversial issue in the UK. Increased use of adjuvant therapy for stage III tumours has occurred over the past decade,[58] contributing to improvements in colorectal cancer survival during the 1990s and early 2000s. There was a slight increase in the proportion of stage III patients in the North West treated with adjuvant chemotherapy (either before or after surgery), from 11.4% in 1997 to 12.7% in 2004 (data not shown). The proportion of stage III patients receiving adjuvant chemotherapy increased for affluent patients between 1997 and 2004, but not for deprived patients (data not shown). It is not clear if these temporal changes may be explained by other factors (stage, comorbitity) but is a further example of highlight differential treatment by socioeconomic groups. Other countries have seen greater improvement in adjuvant therapy than in the England, partially explaining the lower colorectal cancer survival in England.[59] In a population-based study of colorectal cancer patients in the Côte-d'Or region, France, the proportion of patients receiving adjuvant chemotherapy for stage I/II cancers increased from 0.8% in 1976-1987 to 6.4% in 1988-1999, and for stage III cancers from 3.9% to 27.7%.[58] Centralisation of diagnostic and treatment services can ensure consistent provision of adjuvant therapy. In Scotland, a study of adjuvant therapy between 1992 and 1996 found patients admitted to a non-cancer centre were half as

likely to receive adjuvant therapy than if they were treated at a specialist centre.[21] Since this study a number of policies including the Calmine-Hine report,[60] the NHS Cancer Plan 2000[61] and the most recent Cancer Reform Strategy 2007,[62] have improved access to cancer treatment and further centralised cancer services. The introduction of multidisciplinary team meetings has resulted in most patients benefiting from specialist clinical oncology. However, it is clear that there are still socioeconomic disparities in access to chemotherapy.

Chemotherapy toxicity, or adverse effects associated with chemotherapy treatment, influences a patient's likelihood of completing a chemotherapy regime. Adherence to chemotherapy treatment would also be influenced by patient factors, such as transportation, ability to obtain time off work, and general health. The impact of other influences, such as diet, vitamins, positive attitude and fitness, is less tangible, although it is plausible that they could influence adherence to treatment. Cancer registry and HES information on chemotherapy treatment was not detailed enough to determine either the duration of chemotherapy or its timing in relation to surgery (before or after surgery) which is strongly related to both stage and outcome. Patients receiving at least one chemotherapy treatment were designated as having had chemotherapy. As a result, it would be expected that some patients would not complete their full chemotherapy regime, due to side-effects or complications. There is little evidence of socioeconomic variations in adherence and completion of chemotherapy. A population-based study of women with breast cancer in the US between 1998 and 2002 found that adverse events were more likely in women from lower socioeconomic groups.[63] Lower adherence among women from lower socioeconomic groups was attributed to their poorer general health. No variations in chemotherapy toxicity have been found for other patient characteristics, such as ethnicity[64] or age[65]. Socioeconomic variations in chemotherapy toxicity and adherence remain an area for further research.

Surgery type and quality

Over the past decade, rectal cancer survival has improved more rapidly than for colon cancer, mainly due to improvements in surgical techniques. Notable improvements to the quality of treatment in the 1990s and 2000s include the introduction of the multidisciplinary team approach, increasing specialisation of cancer surgeons, the introduction of laparoscopic surgery and the introduction of total mesorectal excision (TME) for rectal cancer. Anterior resection (AR) is the type of surgery for which TME

is a specific technique. Unfortunately, TME is not specifically coded for in HES or cancer registry data. An England-wide study of rectal cancer surgical patients found that the use of AR increased between 1998 to 2004, and coincided with decreased use of abdominoperineal excision (APE) and Hartman's procedure.[8] The England-wide trend reflect the patterns seen in this study, with larger shifts toward the use of AR in affluent than deprived patients (17.5% and 14.6%, respectively). Similarly, in both England and the North West, patients were less likely to receive anterior resection if they were treated at a low-volume hospital or by a low-volume surgeon (data not shown). Trends toward centralisation of services and increased use of anterior resection probably reflect the introduction of multidisciplinary team meetings (MDT). MDT meetings currently discuss most patients and ensure specialist oncology input into treatment plans from a range of specialities (surgery, medical oncology, specialist nurse). A large cancer-registry based study in California found that rectal cancer patients having their surgery at high-volume hospitals were less likely to have had colostomy, and had better survival, than patients treated at other hospitals.[66] A lower proportion of anterior resections would be expected at low-volume hospitals and by low-volume surgeons, because a higher proportion of these patients will receive non-curative and emergency surgery. Despite this, there were still a substantial proportion of patients receiving surgery, particularly anterior resection, at low-volume hospitals and by low-volume surgeons. Poorer survival among low-volume surgeons and low-volume hospitals is a concern for all colorectal cancer surgeries, but particularly for anterior resection (and TME) for which specialist training and teams are necessary to achieve satisfactory surgical results.

Despite equitable access to surgery, in analysis of data after imputation (affluent 89.5% and deprived 87.8%) it is clear there were still socioeconomic variations in the type and quality of surgery. Deprived colorectal cancer patients may be more likely to receive emergency surgery for which outcomes are worse than affluent patients.[8,67] Socioeconomic inequalities in the type of surgery, either emergency or elective, may explain some of the inequalities in outcome. Adjustment for stage (imputed) should have taken into account some, although not all, of the late stage at presentation. Patients presenting as an emergency could be more likely to have blockages which are more common in later stages but can occur at any stage, or due to complications.

Annual hospital case-load and surgeon case-load may not be the ideal measure to evaluate hospital or surgeon patient care, because they may not correlate precisely with the quality of patient care.[66] For example, there may be some very good small surgical units that are categorised along side other low-volume, but poorer-performing, hospitals. In the absence of patient level quality of care data, hospital and surgeon volume provides a reasonable estimate of a surgeons experience and a hospitals peri-operative care. High-volume hospital and surgeon volume has been associated with better survival after colorectal cancer surgery in many studies[66,68,69] although not all.[70,71]

Reductions in socioeconomic variation in the type of operation that a patient receives could be achieved through further centralising treatment in specialised or high-volume centres,[66] thus enabling more equitable access to state-of-the-art treatment (key-hole surgery, TME).[72] Even within specialist centres, it is important to ensure that services are equitable, because variations in treatment type and quality are known to vary within a given hospital.[73] In this research even at very high-volume hospitals, colorectal cancer surgery was conducted by low-volume surgeons in 37.9% of surgeries. Concentrating services may not be possible in all geographies due to logistic barriers[66] but in most Cancer Networks in the UK, it should be achievable.

Survival for elderly cancer patients in the UK has improved, but it remains below that seen in Europe.[74] Despite increasing evidence that elderly patients do not have higher chemotherapy toxicity or surgical complication rates,[65] they are substantially less likely to receive surgery and chemotherapy.[58] In the North West of England the proportion of patients aged 15 to 44 receiving chemotherapy was 73.0% and decreased to 17.2% for patients aged 85 to 99 (Odds ratio after adjustment 0.09). Increasing age was associated with higher levels and severity of comorbid conditions, and with lower survival in the North West of England. Even after adjusting for age and comorbidity older patients were less likely to receive chemotherapy or radiotherapy treatment (Odds ratio for patients aged 85 to 99 after adjustment 0.09 and 0.09, respectively). In other countries, colorectal cancer survival among older patients is much higher than in the UK, raising the question of whether there is some ageism in treating older patients in the UK.

Treatment benefits and survival

Why do deprived patients have lower survival than affluent patients when they are receiving equivalent treatment? In the UK, a randomised controlled trial of

chemotherapy and radiotherapy for colorectal cancer patients diagnosed between 1989 and 1997 found relative survival at five years was the same across all stage, comorbidity and age,[75] but they also ensure consistent and optimal treatment for all patients. Most of the population-based research on inequalities in survival and treatment has been done in the USA, where Medicare databases provide complete treatment data. Clinical trials of survival by ethnic group, which is closely associated with socioeconomic status, have also found that where there is equal access to treatment, the outcomes are similar.[76] Conversely, population-based studies generally find differences in colorectal cancer survival by socioeconomic status (or ethnicity) when patients receive equivalent treatment or after adjusting for treatment.[77,77-79]

Taken together these, studies suggest that the factors associated with inequalities in survival are eliminated in clinical trials, either because of entry criteria (selection) or the consistency of optimal treatment. Furthermore, the similarity of survival by socioeconomic group in clinical trials suggests that once treatment is received (when clinically appropriate), survival is similar in all socioeconomic groups. Ultimately, there is a balance to be met to encourage optimal treatment, whist ensuring over-treatment does not occur.

Greater hospital and surgeon specialisation have been associated with a lower probability of recurrence and better outcomes for colorectal cancer.[66,80] Poorer outcomes for patients treated by low-volume surgeons and low-volume hospitals could be attributed to case-mix. However, socioeconomic inequalities in survival were found at each level of case-load for hospital or surgeon volume, therefore adjustment did not explain socioeconomic inequalities in survival. Post-operative (30-day) mortality was higher for low-volume hospitals and surgeons (9.8%, 10.2%), probably because patients in those settings were more likely to be emergency admissions treated at low-volume hospitals or by low-volume surgeons. Emergency colorectal cancer surgery is associated with advanced disease and bowel obstruction.[81] Even after adjustment for stage, which should account for much of the impact of emergency treatment on survival, and for comorbidity, low-volume hospitals and low-volume surgeons had lower one year and five-year conditional survival. This might suggest that case-mix accounted for some of the excess mortality, whilst surgical type and quality accounted for some. Deprived patients were more likely to have their surgery with a low-volume surgeon, probably either by a low-volume trainee at a high- volume hospital or by a general surgeon at a

low-volume hospital. Temporal patterns of referral and treatment may explain some socioeconomic disparity in survival, particularly if deprived patients have more delays (and longer time). Socioeconomic differences in referral patterns and delay in treatment would be an area of further research.

Private treatment had very little influence on socioeconomic inequalities, because only 2% of patients were treated in the private sector. Relative survival was higher for private patients, although it was only significantly higher for colon cancer patients in the first year after diagnosis. Private patients were a highly biased group: on average younger, and with earlier stage than NHS treated patients. Most private patients received surgery alone (79%) from a moderate-volume NHS surgeon, probably because some surgeons also work both privately and in the NHS. This is an advantage for private patients, because the surgeons experience and training will be maintained by a sufficient range of complexity and volume of surgeries, which would not be available if they operated only in the private sector.

Ideally, ensuring that surgical treatment is optimal for all socioeconomic groups should improve survival for all patients and reduce socioeconomic inequalities in survival. In reality, however there are complex social, resource and health mechanisms which make this unlikely. Support and treatment targeted at deprived patients may be the only way to reduce inequalities in survival, although these would be difficult to implement. Health promotion programmes aimed at the more deprived patients to improve health awareness, decrease obesity and smoking prevalence, and to improve general health could also decrease inequalities, and comorbidity prior to colorectal cancer diagnosis.

Compliance with guidance: access and benefit

Analysis of whether the treatment received was in accordance with clinical guidance was necessarily crude. It was intended as an alternative evaluation of treatment quality, rather than a 'true' reflection of the application of guidance. Receiving treatment in accordance with clinical guidelines is the ideal but individual patient characteristics that could not be measured in this study may influence treatment options (e.g. patient choice, lifestyle), making evaluation of the impact of guidance more complex. Even in this simplistic analysis, however treatment in accordance with guidance identified striking patterns of disparity. Treatment that was compliant with guidance for both colon and rectal cancer patients was progressively less received with increasing

deprivation and age. Higher hospital and surgeon volume was associated with higher levels of treatment in accordance with guidance. Despite being treated in compliance with clinical guidance, there were socioeconomic gaps in survival for both colon and rectal cancer at one year (EHR 1.41 and 1.41). After the first year of diagnosis the socioeconomic inequalities in survival reduced but persisted for colon but not for rectal cancer (EHR 1.22 and 1.11, respectively).

Patients in stage II were most likely to be treated in compliance with clinical guidance for both colon and rectal cancers (96.0%, 97.4%). This may reflect the lower invasiveness of surgery and better general prognosis which could encourage higher levels of active treatment. Alternatively, it may be a artefact of the broad range of treatment regimes clinically appropriate for stage II cancers (e.g. surgery alone, surgery and adjuvant therapy).

The possible reasons for the wide socioeconomic inequalities in survival for patients receiving treatment compliant with clinical guidance mainly relate to treatment type and quality or to external factors (e.g. general health). The inequalities in survival and access for patients who received treatment in compliance with clinical guidance is comparable to those identified in the evaluation of treatment regimes. It is clear that affluent patients receive surgery from higher-volume surgeons and optimal types of surgery than deprived patients, which could contribute to inequalities in survival by treatment regime and clinical guidance. Furthermore if similar type and quality of treatment was received by each socioeconomic group very narrow socioeconomic inequality in survival would be expected, as has been achieved in clinical trials.[82] Whilst, the influence of external factors and means to address these have been described previously.

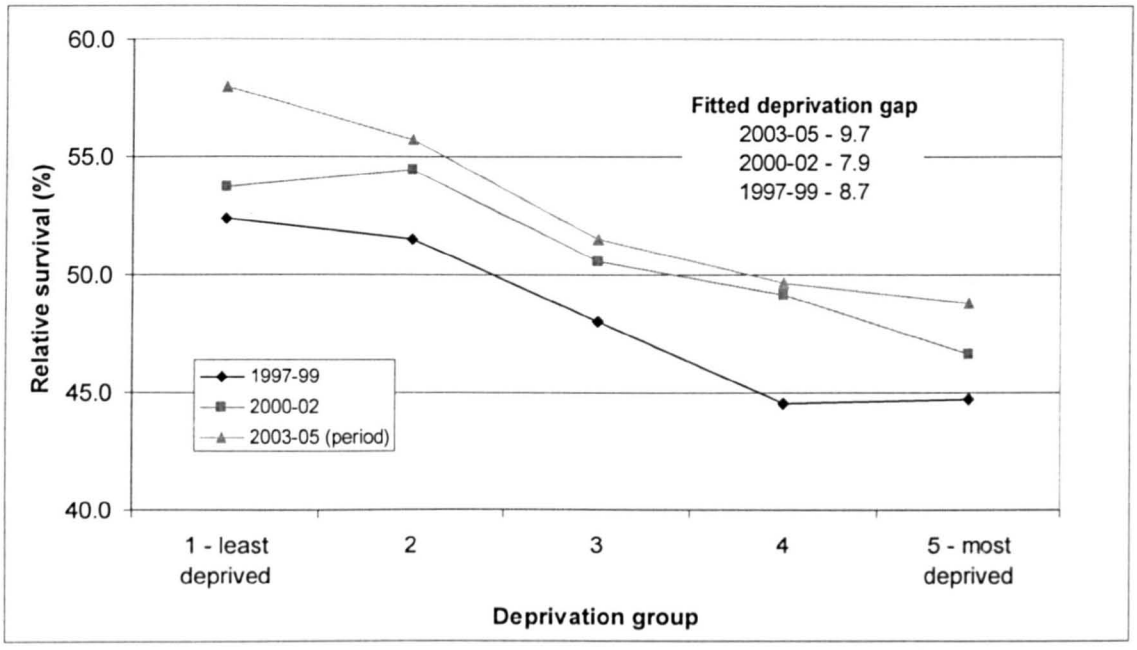
Future and screening

Improvements in colorectal cancer survival since the mid-1990s have been attributed to better surgical techniques, post-operative care and adjuvant therapy. In the next decade, survival is likely to improve further with increased use of laparoscopic (key-hole) surgery. Deprived patients in the North West were less likely to receive treatment in accordance with guidance and optimal treatment. If inequitable access to the most modern treatment regimes persists, socioeconomic inequalities in survival are likely to occur in the future.[60,83]

Lower up-take of colorectal screening among the deprived than the affluent is evident in the UK pilot[84] and the North West colorectal screening programmes.[85] The national colorectal screening programme for 60 to 69 year olds, based on the faecal occult blood test (FOB), began in April 2006 and will achieve national coverage by 2009. Merseyside and Cheshire was one of the first regions to begin screening in 2006 (achieving regional coverage in 2008). So far screening has detected 292 cancers with 50% in stage I (as at 3 Nov 2008). However, there are large socioeconomic variations in FOB up-take, from 28% in deprived areas to 60-70% in wealthy areas. Variations in the socioeconomic up-take of population-based breast cancer screening programmes have resulted in increases in inequalities in survival in Eindhoven, Netherlands[86] but a narrowing occurred in Scotland.[87] Mammographic screening up take rates are much higher (up to 76%)[86,88] and show less variation between deprived and affluent areas (58% to 80%) than in the Merseyside and Cheshire colorectal screening programme. Such large inequalities in FOB up take are likely to widen inequalities in survival among the screening age group, and the 70 to 79 age group at least in the period immediately after the introduction of screening.

In the absence of screening, the deprivation gap in five-year relative survival for the North West is expected to increase from 7.7% of patients diagnosed in 1997-99 to 9.2% of patients diagnosed in 2003-05 (Figure 9.3). The initial analysis plan for this research included evaluation of time trends, developing methods for excess hazard models for the hybrid survival approach, and future estimates of survival, but shifted toward more in depth analysis of treatment patterns. Brief hybrid survival estimates are presented here in order to support hypothesis about future socioeconomic inequalities in survival. Estimates for patients diagnosed during 2003-05 were based on the hybrid approach (with follow-up to 2007).[89] Improvements in surgery and adjuvant therapy may continue to improve survival for all socioeconomic groups but the largest increases in five-year relative survival will occur in the affluent, improving from 52% in 1997-99 to 58% in 2003-05 (from deprived 44.7% in 1997-1999 to 49% in 2003-2005) in the deprived. Even ten years after diagnosis, a deprivation gap of 7% was predicted for patients diagnosed between 2003 and 2005 (based on hybrid relative survival approach). The socioeconomic inequalities in survival in the North West are similar to those expected for England for the same time periods.[2,90]

Figure 9.3: Relative survival at 5 years by period of diagnosis (cohort survival for 1997-2002, hybrid survival approach 2003-07), colorectal cancer, North West of England



Limitations of the data

Limitations to the interpretability of this research and to its generalisability, have been addressed throughout the discussion. The following remarks will focus solely on data limitations. Demographic and diagnostic information held by cancer registries is generally very robust and complete, but information on stage, grade and treatment is less complete, particularly for older patients.[12,91] For example, increasing age was associated with a higher proportion of Death Certificate Only (DCO) registrations in cancer registry data. The lack of a diagnosis date (or record of treatment) has been attributed both to lower levels of treatment and to incomplete registry data.[91] Exclusion of DCO registrations and age adjustment within survival analysis can decrease, but not remove the influence of age-specific differences in under-ascertainment.[92] The number and proportion of DCO cases has been decreasing since the mid 1990s, because of improved collection and linkage of treatment and death data (improved IT and database capabilities). In the early 2000s, receipt of palliative care data decreased the number of DCO registrations in the North West of England cancer registry (NWCIS).

In order to improve the completeness of treatment information, cancer registry and HES data were linked, thereby achieving a linkage for 82% of colorectal cancer patients. Complete linkage (100%) between HES and cancer registry data is unrealistic, because of missing demographic information, particularly NHS number in HES. Demographic

information was generally less complete in HES, but it has been improving with time, probably because of improvements in training and knowledge of clinical coding personnel, improvements in information technology and emphasis on measuring activity through HES (and its precursor, the patient administration system). The overall linkage of 82% achieved in this study was similar to that achieved in other studies of testis and prostate cancer in London and South West England (63%),[93] teenagers and young adults in England (86%),[94] and rectal cancer patients undergoing abdominoperineal excision in England (92%).[8] Cancer patients who could not be linked to HES included both those with incomplete demographic information and patients who did not attend hospital.

The method of multiple imputation was used to provide a dataset for analysis with estimates of the missing data, particularly for stage and treatment data. Imputation is a widely used method for handling datasets with missing data in order to improve the interpretability of results,[95-99] although survival analysis was rarely been done with imputed data.[82,96] Imputation requires assumptions about the mechanism of missingness and the patterns and associations of missingness. For cancer registry data, the variables associated with missing stage and treatment are well documented[12,91,100,101] providing support to the assumption that the mechanism of missing data was Missing at Random assumption (MAR), but it is not possible to test these assumptions. Most variables with missing data generally had a moderate level of missing data (10% to 40%), but the proportion of patients with missing chemotherapy data was high (63%). Whilst this is far from ideal, the imputation method appeared to manage these missing data for chemotherapy well, resulting in logical overall analyses consistent with other studies,[8,66,102] probably because of the close association between chemotherapy and stage. Overall, the improvement of data completeness by linkage to HES and multiple imputation appears to have adequately managed missing data.

Obtaining complete treatment information would enable more detailed analysis and useful conclusions. Information on the type of chemotherapy regime (neo-adjuvantly, adjuvantly and adherence) and surgical intent (curative, palliative, emergency, elective) would be invaluable in disentangling inequalities in treatment and survival. While cancer treatment information is increasingly being obtained from HES or Cancer registry data (but rarely both) this does not provide the detailed information necessary for analysis of surgical intent and chemotherapy regime. It is very difficult to obtain this information in a standard and comparable format from multiple hospitals however there

are currently a number of initiatives to improve data completeness and quality. The main limitation is obtaining timely treatment information in electronic format with consistent information from all trusts. This is being addressed by i) mandating electronic data provision ii) collection of data at MDT through real time computer systems. It will take a few years before this dataset will be complete.

Geographic (ecological) measures of socioeconomic status will always result in some misclassification of individuals because one socioeconomic status may not be representative of all individuals living in that geography, commonly known as the 'ecological fallacy'. This would result in attenuation of socioeconomic gradients in survival, thus raising or lowering the socioeconomic-specific survival. Additionally, exposure to risk factors for colorectal cancer may also occur decades before diagnosis and at a time when the patient was in another socioeconomic group (and geography). However, any temporal shifts probably have a small influence, because of the strong association between socioeconomic status and cancer incidence. The use of geographic measures of socioeconomic status is a practical choice for epidemiological studies and measures are generally consistent over time.[103]

Summary

This research appears to be the first population-based analysis of inequalities in colorectal cancer with complete stage and treatment information obtained through a combination of both multiple data sources and multiple imputation. This unique analysis highlighted the less than optimal outcomes and survival in deprived patients compared to affluent.

Colorectal cancer treatment and survival is improving, but deprived patients continue to have less than optimal treatment and worse survival than affluent patients. Deprived patients appear to have higher levels of factors that may limit their treatment options, such as comorbid conditions. Even after taking these factors into account, however deprived patients still received less optimal treatment (e.g. less adjuvant therapy). The factors contributing to these inequalities in treatment are complex including physical, social, lifestyle and clinical domains. The most effective way to reduce socioeconomic disparities in treatment and survival may be targeted health programmes aimed at mandating optimal treatment for all patients rather than preferential treatment for deprived patients.

How could socioeconomic inequalities in survival be reduced?: recommendations for policy and service developments

The socioeconomic variations in surgery type and adjuvant therapy reported above could not be explained by clinical or demographic factors. Initiatives to encourage equality of treatment are probably the only way to reduce socioeconomic variations in treatment, and ultimately socioeconomic inequalities in survival. Policies to ensure that deprived patients receive optimal treatment, possibly through systems that required justification of treatment plans that were not in accordance with clinical guidance could reduce socioeconomic inequalities. Centralisation of services and the implementation of the current clinical guidance have improved survival, but have not reduced inequalities in treatment or survival. Requiring justification of exceptions to optimal treatment and clinical guidance would ensure all patients are receiving optimal treatment, except when not clinically appropriate. Entering a higher proportion of deprived patients in clinical trials may also narrow inequalities and ensure consistent optimal treatment. However, any increases in entry to clinical trials may occur more rapidly in affluent patients. Furthermore, inclusion criteria (particularly comorbidity) may mean higher proportions of affluent than deprived patients are eligible for entry. Despite the difficulties increasing the proportion of deprived patients in clinical trials may narrow inequalities because there were no socioeconomic inequalities in survival for colorectal cancer patients treated in clinical trials. Further studies would be helpful in supporting policy development, particularly detailed evaluations of treatment type and quality, specifically with details on chemotherapy toxicity, adherence, type of surgery and complications.

Delays in access to treatment within the patient pathway should be investigated. Deprived patients were more likely than affluent patients to receive surgery from a low-volume surgeon. It is likely that most of the surgery by low-volume surgeons is emergency surgery, highlighting the need for greater symptom awareness and earlier stage at diagnosis among deprived patients. Symptom awareness may be improved through general health campaigns (e.g. 'five a day') and the bowel screening programme, but further effort is probably needed to target deprived communities.

Patient- or system-led delays in the patient pathway may contribute to delays in diagnosis, increased levels of complication and decreased adherence to treatment regime. Reducing delays could be a relatively simple way to improve the timeliness of treatment: although this is of benefit to the individual patient, the impact (if any) on

population-based survival remains unquantified. From the data available, it is not possible to evaluate patient pathways or referral patterns to determine if there were socioeconomic variations in referral to a specialists or delays. For deprived patients the referral pathway (and any delays) is of particular importance to treatment at a specialist hospital, but more importantly by a high-volume surgeon.

Further analysis of patients pathways is possible if the data quality and completeness of treatment and staging information is improved. There is strong support from clinician groups to collect detailed treatment information (e.g. emergency surgery, curative surgery, neo-adjuvant and adjuvant therapy) but in order for large population based studies to be conducted this data must be consistent across all trusts and in an electronic format. The cancer reform strategy[62] mandated data provision of electronic by trusts to cancer registries by 2011 but did not clearly define the completeness of submissions. Many trusts are making good progress towards submitting but the information is frequently incomplete. For example a submission might include the name and address of a patient seen at MDT but no information on treatment plan, or stage. In order to collect detailed treatment information clear targets and resources must be applied with the support of clinical groups. Regular and timely feedback also be done to ensure continued interest.

The introduction of population-based screening may increase inequalities, at least temporarily, through earlier stage at diagnosis in affluent rather than deprived patients. Affluent people were at least 10% more likely to complete and return the Faecal Occult Blood test.[84,85] Although, population-based bowel screening is currently limited to 60-69 year olds, (with over 70s upon request) screening will influence both the incidence and mortality rates in older age groups, because cancers are detected earlier in a younger age group. Initiatives to increase the proportion of deprived people completing the FOB are vital to restrict this probable widening of socioeconomic inequalities in diagnosis and survival.

Conclusion

- This appears to be the first large population-based study on colorectal cancer to include data on comorbidity and stage data. Complete data on stage and treatment have always been difficult to obtain for population-based cancer registries. By using both cancer registry and hospital episode data, to obtain

information on surgery and chemotherapy data, the proportion of patients receiving surgery was more complete and comparable with clinical studies.

- The use of administrative databases to measure comorbidity in population-based data, such as cancer registry data, is a choice of practicality and feasibility. Some residual confounding is likely to remain due to under-ascertainment of comorbidity. The comorbidity measures and the time period within which the comorbid conditions are identified in relation to the cancer diagnosis should also be considered and evaluated in relation to the disease under study. The Charlson comorbidity measure derived from the period 18 months to 6 months before colorectal cancer diagnosis strongly predicted cancer-related mortality in the first year after a diagnosis. Even after adjusting for comorbidity, the strongest predictors of cancer-related mortality were stage and age. Adjustment for comorbidity should generally be encouraged, to enable more realistic and clinically appropriate and comparable estimates of survival for cancer.

- The survival advantage in affluent patients has generally been attributed to earlier stage at diagnosis and fewer comorbid conditions, but both are incompletely recorded in most population-based data. A major strength of this study is the lack of missing stage and comorbidity data, obtained by a combination of data linkage and imputation. This allowed complete adjustment and evaluation of survival for 29,563 colorectal cancer patients diagnosed in the North West of England between 1997 and 2004. Advanced stage and greater comorbidity were both strongly associated with poor survival, but they did not explain the socioeconomic inequalities in survival. Most of the excess mortality occurred in the first year after diagnosis and was frequently attributed to post-operative mortality, late stage at diagnosis, comorbid conditions and other complications. The deprivation gap in survival appeared to be 'set' in the first year after diagnosis, remaining similar up to five years after diagnosis. Inequalities in colorectal cancer survival have been found in other countries. Whilst these findings were based on patients diagnosed in the North West the underlying pattern is likely to be generalisable to the UK, and possibly Europe.

- Equitable access to treatment is a fundamental principle of the NHS and was a central conclusion of the Calmine-Hine report. It is difficult to ascertain if equal

access is occurring, because whether treatment was clinically appropriate can't be assessed without complete information (stage, comorbidity and treatment). In this study, there was considerable socioeconomic inequality in treatment, with deprived patients receiving less adjuvant therapy than affluent, and a higher proportion receiving no treatment. More modern surgical techniques, such as anterior resection, were less likely to be performed on deprived patients. Modern surgical type, lower post-operative mortality and higher survival are associated with surgery conducted by high-volume surgeons and in high-volume hospitals, but the chance of receiving surgery from a high-volume surgeon reduced with increasing deprivation. Overall, deprived patients were less likely to receive optimal treatment, even after adjustment for stage and comorbidity. This raises the key questions: i) What are the barriers to treatment for deprived patients? And ii) are there other factors which could not be evaluated in this study, but which may explain the treatment differences?

- Even if deprived and affluent patients received equivalent treatment, there was still a deprivation gap in survival at one year. Deprived patients had higher post-operative mortality and excess mortality for high-volume surgeon and high-volume hospitals. Even when deprived patients received the same treatment type as affluent patients, inequalities in survival were observed. This could be because of treatment factors that could not be measured in this study (e.g. chemotoxicity, timeliness of treatment) or other risk factors for mortality or complications (e.g. obesity, smoking). Evaluation of treatment regimes using population-based data may not have the depth of detail to account for the complexity of the entire treatment pathway, but it does provide a population-based analysis that can be studied with more in-depth clinical audits.

- Ideally, population-based data should be complete, avoiding the need for the arduous linkage process and the use of multiple imputation. Cancer registry data is known to be of high quality for demographic and tumour details, but the data quality of hospital episode data is of lower quality and completeness. Multiple imputation is a widely used and robust technique, but it is always preferable to have original data that are complete. This enables more in-depth analysis than was possible here for surgery types.

- Throughout the study period of 1997 to 2004 clinical guidelines for the treatment of colon and rectal cancer have existed, and remained similar during the entire period. Therefore, with the optimal treatment regimes clearly identified it is particularly disappointing to find socioeconomic inequalities in survival during this period. This research adjusted for patient factors and still found socioeconomic variations in treatment and survival still persisted. The persistence of socioeconomic variations suggests intervention to mandate optimal treatment for all patients involving both health policy and clinical guidance may narrow the inequalities.
- The treatment a colorectal cancer patient receives appears to depend, in part, on socioeconomic status. This may be due to the treating physician judgements of the patients perceived ability to withstand a given treatment regime. Ensuring equal access to services and equal improvement in survival across all social groups will be a continuing challenge for the NHS. The introduction of a colorectal cancer screening programme will probably increase inequalities in survival, because up-take rates are higher among the affluent. Ultimately, a universal health-care system may not be able to achieve equal survival, because of external factors that cannot be controlled, but ensuring equitable access would be expected to greatly reduce the inequalities in colorectal cancer survival.

Publications

A number of publications have been, or are in the process of being written, as a result of the work in this thesis.

1. Final drafting prior to submission to the International Journal of Epidemiology.

   Modelling relative survival in the presence of incomplete data: a tutorial

   Nur U[1],Shack LG[1,2], Rachet B[1], Carpenter JR[3] and Coleman MP[1]
   [1] CRUK Survival Group, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT
   [2] North West Cancer Intelligence Service, Christie Hospital NHS Foundation Trust, Wilmslow Road, Manchester, M20 4RX
   [3] Medical Statistics Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT

2. This paper is currently being redrafted for planned submission to Journal of Epidemiology and Community health. It was submitted but declined from the Journal of Clinical Epidemiology.

   Colorectal cancer survival and comorbidity: does the choice of comorbidity indicator matter?

   Shack LG[1,2*], Rachet B[2], Williams EMI[3], John Northover[4], Coleman MP[2]
   [1] North West Cancer Intelligence Service, Christie Hospital NHS Foundation Trust, Wilmslow Road, Manchester, M20 4RX
   [2] CRUK Survival Group, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT
   [3] Division of Public Health, School of Population, Community and Behavioural Sciences, Whelan Building, University of Liverpool, Liverpool L69 3GB
   [4] Imperial College of Science, Technology and Medicine, St Mark's Hospital, Watford Road, Harrow, HA1 3UJ

3. The following papers are currently being drafted:

   a. Estimates of 'cure' after colorectal cancer: variations by stage and age.

   b. Socioeconomic inequalities in colorectal survival are not explained by stage and comorbidity.

4. I also intend to write papers based on the main results of Chapters 7 and 8

Reference List

(1) Coleman MP, Rachet B, Woods LM, Mitry E, Riga M, Cooper N, Quinn MJ, Brenner H, Estève J. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *British Journal of Cancer.* 2004; 90:1367-1373.

(2) Mitry E, Rachet B, Quinn M, Cooper N, Coleman MP. Survival from cancer of the colon in England and Wales up to 2001. *British Journal of Cancer.* 2008; 99:s26-s29.

(3) Link BG, Phelan JC, Mieck R, Westin EL. The resources that matter: Fundamental social causes of health disparities and the challenge of intelligence. *Journal of Health and Social Behaviour.* 2008; 49:72-91.

(4) Link BG, Phelan JC. Social conditions as fundamental causes of disease. *Journal of Health and Social Behaviour.* 1995; Spec:80-94.

(5) Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. *Annals of Oncology.* 2006; 17:5-19.

(6) NYCRIS. *Cancer treatment policies & their effects on survival; colorectal.* Leeds: NYCRIS, 2000.

(7) Birkmeyer JD, Siewers AE, FInlayson EVA, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE. Hospital volume and surgical mortality in the United States. *The New England Journal of Medicine.* 2002; 346:1127-1137.

(8) Morris E, Quirke P, Thomas JD, Fairley L, Cottier B, Forman D. Unacceptable variation in abdominoperineal excision rates for rectal cancer: time to intervene? *Gut.* 2008; 12:1690-1697.

(9) Brewster DH, Thomson CS, Hole DJ, Black RJ, Stroner PL, Gillis CR. Relation between socioeconomic status and tumour stage in patients with breast, colorectal, ovarian and lung cancer: results from four national, population based studies. *British Medical Journal.* 2001; 322:830-831.

(10) De Marco MF, Janssen-Heijnen MLG, van der Heijden LH, Coebergh JWW. Comorbidity and colorectal cancer according to subsite and stage: a population-based study. *European Journal of Cancer.* 2000; 36:95-99.

(11) Green J, Watson J, Roche M, Beral V, Patnick J. Stage, grade, and morphology of tumours of the colon and rectum recorded in the Oxford Cancer Registry, 1995-2003. *British Journal of Cancer.* 2007; 96:140-142.

(12) Adams J, White M, Forman D. Are there socioeconomic gradients in the quality of data held by registries? *Journal of Epidemiology and Community Health.* 2004; 58:1052-1053.

(13) Schrijvers C, Mackenbach JP, Lutz J-M, Quinn M, Coleman MP. Deprivation, stage at diagnosis and cancer survival. *International Journal of Cancer.* 1995; 63:324-329.

(14) Ionescu MV, Carey F, Tait IS, Steele RJC. Socioeconomic status and stage at presentation of colorectal cancer. *Lancet.* 1998; 352:1439.

(15) Frederiksen BL, Osler M, Harling H, on behalf of Danish Colorectal Cancer Group and T Jorgensen. Social inequalities in stage at diagnosis of rectal but not colonic cancer: a nationwide study. *British Journal of Cancer.* 2008; 98:668-673.

(16) Adams J, White M, Forman D. Are there socioeconomic gradients in stage and grade of breast cancer at diagnosis? Cross sectional analysis of UK cancer registry data. *British Medical Journal.* 2004; 329:142-143.

(17) Downing A, Prakash K, Gilthorpe MS, Stefoski MJ, Forman D. The effect of socioeconomic background on stage at diagnosis, treatment pattern and survival in women with invasive breast cancer. *British Journal of Cancer.* 2007; 96:836-840.

(18) Kaffashian F, Godward S, Davies T, Soloman L, McCann J, Duffy SW. Socioeconomic effects on breast cancer survival: proportion attributable to stage and morphology. *British Journal of Cancer.* 2003; 89:1693-1696.

(19) Astler VB, Coller FA. The prognostic significance of direct extension of carcinoma of the colon and rectum. *Annals of Surgery.* 1954; 139:846.

(20) Morris E, Maughan NJ, Forman D, Quirke P. Identifying stage III colorectal cancer patients: The influence of the patient, surgeon and pathologist. *Journal of Clinical Oncology.* 2007; 25:2573-2579.

(21) Pitchforth E, Russell E, Van der Pol M. Access to specialist cancer care: it it equitable? *British Journal of Cancer.* 2002; 87:1221-1226.

(22) Pheby DFH, Levine DF, Pitcher RW, Shepard NA. Lymph node harvests directly influence the staging of colorectal cancer: evidence from a regional audit. *Journal of Clinical Pathology.* 2004; 57:43-47.

(23) Shahrier M, Ahnen DJ. Colorectal cancer survival in Europe: the Will Rogers phenomenon revisted. *Gut.* 2000;463-468.

(24) Feinstein AR, Sosin DM, Wells Ck. The Will Rogers phenomenon. Stage migration and new diagnostic techniquest as a source of misleading statistics for survival in cancer. *New England Journal of Medicine.* 1985; 312:1604-1608.

(25) Ciccolallo L, Capocaccia R, Coleman MP, Berrino F, Coebergh JWW, Damhuis RAM, Faivre J, Martinez-Garcia C, Møller H, Ponz de Leon M et al. Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. *Gut.* 2005; 54:268-273.

(26) Jestin P, Påhlman L, Glimelius B, Gunnarsson U. Cancer staging and survival in colon cancer is dependent on the quality of the pathologists' specimen examination. *European Journal of Cancer.* 2005; 41:2071-2078.

(27) Tilney HS, Tekkis PP, Heriot AG, Lovegrove RE, Smith JJ, Thompson MR, Stamatakis JD, on behalf of the Association of Coloproctology of Great Britian and Ireland. *Report of the National Bowel Cancer Audit Project "Assessing Quality".* London: The Association of Coloproctology of Great Britian and Ireland, 2006.

(28) Munro AJ, Bentley AHM. Deprivation, comorbidity and survival in a cohort of patients with colorectal cancer. *European Journal of Cancer Care.* 2004; 13:262.

(29) SEER. Surveillance Epidemiology and End Results. 2006. (cited 1 Sept. 2006) Available from URL: **http://seer.cancer.gov/**

(30) Nuttal M, van der Meulen J, Emberton M. Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. *Journal of Clincal Epidemiology.* 2006; 59:265-273.

(31) Faivre-Finn C, Bouvier-Benhamiche AM, Phelip JM, Manfredi S, Dancourt V, Faivre J. Colon cancer in France: evidence for improvement in management and survival. *Gut.* 2002; 51:60-64.

(32) Janssen-Heijnen MLG, Maas HA, Houterman S, Lemmons VEPP, Rutten HJT, Coebergh JW. Comorbidity in older surgical cancer patients: influence on patient care and outcome. *European Journal of Cancer.* 2007; 43:2179-2193.

(33) Yancik R, Wesley MN, Ries LAG, Havlik RJ, Long S, Edwards BK, Yates JW. Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients. *Cancer.* 1998; 82:2123-2134.

(34) Schrijvers C, Coebergh J, Mackenbach JP. Socioeconomic status and comorbidity among newly diagnosed cancer patients. *Cancer.* 1997; 80:1482-1488.

(35) Gross CP, McAvay GJ, Krumholz HM, Paltiel AD, Bhasin D, Tinetti ME. The effect of age and chronic illness on life expectancy after a diagnosis of colorectal cancer: implications for screening. *Annals of Internal Medicine.* 2006; 145:646-654.

(36) Garout M, Tilney HS, Tekkis PP, Ayala A. Comparison of administrative data with the Association of Coloproctology of Great Britian and Ireland (ACPGBI) colorectal cancer database. *International Journal of Colorectal Disease.* 2008; 23:155-163.

(37) Aylin P, Bottle A, Majeed A. Use of administrative data or clinical databases as predictors of risk of death in hospital: comparison of models. *British Medical Journal.* 2007; 334:1044-1051.

(38) Wood J, Hennell T, Jones A, Hooper J, Tocque K, Bellis MA. *Where wealth means health: Illustrating inequalities in the North West.* Liverpool: North West Public Health Observatory, 2006.

(39) Chan AO, Jim MH, Lam KF, Morris JS, Sui DC, Tong T, Ng FH, Wong SY, Hui WH, Chan CK et al. Prevalence of colorectal neoplasm among patients with newly diagnosed coronary artery disease. *Journal of the American Medical Association.* 2007; 298:1412-1419.

(40) Klabunde CN, Legler JM, Warren JL, Baldwin LM, Schrage D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal and lung cancer patients. *Annals of Epidemiology.* 2007; 17:584-590.

(41) Yorkshire and Humberside Public Health Observatory. Estimating diagbetes diagnosis rates using QOF data. 2008. (cited 11 Dec. 2008)

(42) Halbert RJ, Isonaka S, George D, Iqbal A. Interpreting COPD prevalence estimats: What is the true burden of disease? *Chest.* 2003; 123:1684-1692.

(43) Hamer M, Stamatakis E, Saxton JM. The impact of physical activity on all-cause mortality in men and women after a cancer diagnosis. Cancer Causes and Control. In press 2008.

(44) Dray X, Boutron-Ruault MC, Bertrais S, Saphinho D, Benhamiche-Bouvier AM, Faivre J. Influence of dietary factors on colorectal cancer survival. *Gut.* 2003; 52:868-873.

(45) Carmicheal AR. Obesity and prognosis of breast cancer. *Obesity Review.* 2006; 7:333-340.

(46) Dignam JJ, Polite BN, Yothers G, Raich P, Colangelo L, O'Connel MJ, Wolmark N. Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. *Journal of the National Cancer Institute.* 2008;1647-1654.

(47) Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, Nelson H, Whittom R, Hantel A, Thomas J, Fuchs CS et al. Impact of body mass index and weight change after treatment on cancer recurrence and survival in patients with stage III colon cancer: findings from Cancer and Leukemia Group B 89803. *Journal of Clinical Oncology.* 2008; 26:4109-4115.

(48) Munro AJ, Bentley AHM, Ackland C, Boyle P. Smoking compromises cause-specific survival in patients with operable colorectal cancer. *Clinical Oncology.* 2006; 18:436-440.

(49) Nickelson TN, Jorgensen T, Kronborg O. Lifestyle and 30-day complications to surgery for colorectal cancer. *Acta Oncology.* 2005; 44:218-223.

(50) Moeller H, Shack L, Moran A. *Lung cancer in the North West.* Manchester: NWCIS, 2008.

(51) Gatta G, Ciccolallo L, Capocaccia R, Coleman MP, Hakulinen T, Møller H, Berrino F, and the EUROCARE Working Group. Differences in colorectal cancer survival between European and UK populations: the importance of sub-site and morphology. *European Journal of Cancer.* 2008; 39:2214-2222.

(52) Gatta G, Capocaccia R, Sant M, Bell J, Coebergh J, Damhuis RAM, Martines-Garcia C, Pawlega J, Ponz de Leon M, Pottier D et al. Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high-resolution study. *Gut.* 2000; 47:533-538.

(53) Thomson CS, Hole D, Twelves CJ, Brewster DH, Black R, on behalf of the Scottish Cancer Therapy Network. Prognostic factors in women with breast cancer: distribution by socioeconomic status and effect on differences in survival. *Journal of Epidemiology and Community Health.* 2001; 55:315.

(54) Schottenfeld D, Winawer SJ. Cancers of the large intestine. In: Schottenfeld D, Fraumeni JF Jr, editors. *Cancer Epidemiology and Prevention.* 2nd ed. Oxford: Oxford University Press, 1996, 813-840.

(55) Jeter JM, Kohlmann W, Gruber SB. Genetics of colorectal cancer. *Oncology.* 2006; 20:269-276.

(56) Ashktorab H, Smoot DT, Farzanmehr H. Clinicopathological features and microsatellite instability (MSI) in colorectal cancers from African Americans. *International Journal of Cancer.* 2005; 116:914-919.

(57) Carethers JM, Smith EJ, Behling CA. Use of 5-fluorouracil and survival in patients with microsatellite-unstable colorectal cancer. *Gastroenterology.* 2004; 126:394-401.

(58) Mitry E, Bouvier AM, Estève J, Faivre J. Improvement in colorectal cancer survival: A population-based study. *European Journal of Cancer.* 2005; 41:2297-2303.

(59) Sant M, Capocaccia R, Coleman MP, Berrino F, Gatta G, Micheli A, Verdecchia A, Faivre J, Hakulinen T, Coebergh JW et al. Cancer survival increases in Europe, but international differences remain wide. *European Journal of Cancer.* 2001; 37:1659-1667.

(60) Expert Advisory Group on Cancer. *A policy framework for commissioning cancer services: a report by the Expert Advisory Group on cancer to the Chief Medical Officers of England and Wales.* London: Department of Health, 1995.

(61) Department of Health. *The NHS Cancer Plan.* London: Department of Health, 2000.

(62) Department of Health. *Cancer Reform Strategy.* London: Department of Health, 2007.

(63) Hasset MJ, O'Malley AJ, Pakes JR, Newhouse JP, Earle CC. Frequence and costs of chemotherapy-related serious adverse effect in a populatin sample of women with breast cancer. *Journal of the National Cancer Institute.* 2006; 98:-1108.

(64) Shavers VL, Brown ML. Racial and ethnic disparities inthe receipt of cancer treatment. *Journal of the National Cancer Institute.* 2002; 94:334-357.

(65) Golfinopoulos V, Pentheroudakis G, Pavlidis N. Treatment of colorectal cancer in the elderly: a review of the literature. *Cancer Treatment Reviews.* 2006; 32:1-8.

(66) Hodgson DC, Zhang W, Zaslavsky AM, Fuchs C, Wright WE, Ayanian JZ. Relation of hospital volume to colostomy rates and survival for patients with rectal cancer. *Journal of the National Cancer Institute.* 2003; 95:708-716.

(67) Pollock A, Vickers N. Deprivation and emergency admissions for cancers of colorectum, lung, and breast in south east England: ecological study. *British Medical Journal.* 1998; 317:245-252.

(68) Blomqvist P, Ekbom A, Nyrén O, Krusemo UB, Bergström R, Adami HO. Survival after rectal cancer: differences between hospital catchment areas. A nationwide study in Sweden. *Gut.* 1999; 45:39-44.

(69) Renzulli P, Lowy A, Maibach R, Egeli RA, Metzger U, Laffer UT. The influence of the surgeon's and the hospital's caseload on survival and local recurrence after colorectal cancer surgery. *Journal of Surgery.* 2006; 139:296-304.

(70) Parry JM, Collins S, Mathers J, Scott NA, Woodman CBJ. Influence of volume of work on the outcome of treatment for patients with colorectal cancer. *British Journal of Surgery.* 1999; 86:475-481.

(71) McArdle CS, Hole DJ. Outcome following surgery for colorectal cancer: analysis by hospital after adjustment for case-mix and deprivation. *British Journal of Cancer.* 2002; 86:331-335.

(72) Menviellle G, Kunst A. Social inequalities in cancer incidence and cancer survival: Lessons from Danish studies. *European Journal of Cancer.* 2008; 44:1933-1937.

(73) Duxbury MS, Brodribb AJ, Oppong FC, Hosie KB. Management of colorectal cancer: variations in practice in one hospital. *European Journal of Surgical Oncology.* 2003; 29:400-402.

(74) Quaglia A, Tamilla A, Shack L, Brenner H, Janssen-Heijnen MLG, Allemani C et al. The cancer survival gap between elderly and middle aged patients in europe is widening. European Journal of Cancer. In press 2009.

(75) Vardy J, Tannock IF. Quality of cancer care. *Annals of Oncology.* 2004; 15:1001-1006.

(76) Polite BN, Dinham JJ, Olopade OI. Colorectal cancer model of health disparities: understanding mortality differences in minority populations. *Journal of Clinical Oncology.* 2006; 24:2179-2187.

(77) Dominitz JA, Samsa GP, Landsman P, Provenzale D. Race, treatment, and survival among colorectal carcinoma patients in an equal-access medical system. *Cancer.* 1998; 82:2312-2320.

(78) Alexander D, Chatla C, Funkhouser E. Postsurgical disparity in survival between African Americans and Caucasians with colonic adenocarinoma. *Cancer.* 2004; 101:66-76.

(79) Wudel LJ, Chapman WC, Shyr Y. Disparate outcomes in patients with colorectal cancer: Effect of race on long-term survival. *Archivees of Surgery.* 2002; 137:550-554.

(80) Grilli R, Minozzi S, Tinazzi A, Labianca R, Sheldon TA, Liverati A. Do specialists do it better? The impact of specialization on the processes and outcomes of care for cancer patients. *Annals of Oncology.* 1998; 9:365-374.

(81) Jestin P, Nilsson J, Heurgren M, Påhlman L, Glimelius B, Gunnarsson U. Emergency surgery for colonic cancer in a defined population. *British Journal of Surgery.* 2004; 92:94-100.

(82) Nur U, Rachet B, Parmar MKB, Sydes MR, Cooper N, Lepage C, Northover J, James R, Coleman MP, on behalf of the AXIS collaborators. No socioeconomic inequalities in colorectal cancer survival within a randomised clinical trial. *British Journal of Cancer.* 2008; 99:1923-1928.

(83) Silman AJ, Evans SJ. Regional differences in survival from cancer. *Community Medicine.* 1981; 3:291.

(84) UK Colorectal Cancer Screening Pilot Group. Results of the first round of demonstration pilot of screening from colorectal cancer in the United Kingdom. *British Medical Journal.* 2004; 329:133-135.

(85) Coughlin M, Mackenzie P, Sayer M. Merseyside colorectal cancer screening programme. Shack L, Milner S, editors. 2008.

(86) Louwman WJ, van de Poll-Franse LV, Fracheboud J, Roukema JA, Coebergh J. Impact of a programme of mass mammography screening for breast cancer on socio-economic variation in survival: a population-based study. *Breast Cancer Research and Treatment.* 2007; 105:369-375.

(87) Shack LG, Rachet B, Brewster DH, Coleman MP. Socioeconomic inequalities in cancer survival in Scotland 1986-2000. *British Journal of Cancer.* 2007; 97:999-1004.

(88) NHS. NHS breast screening programme. 2007. (cited 20 Apr. 2007) Available from URL: www.cancerscreening.nhs.uk/breastscreening

(89) Brenner H, Rachet B. Hybrid analysis for up-to-date long-term survival rates in cancer regsitries with delayed recording of incident cases. *European Journal of Cancer.* 2004; 40:2494-2501.

(90) Mitry E, Rachet B, Quinn M, Cooper N, Coleman MP. Survival from cancer of the rectum in England and Wales up to 2001. *British Journal of Cancer.* 2008; 99:s30-s32.

(91) Adams J, Audisio RA, White M, Forman D. Age-related variations in progression of cancer at diagnosis and completeness of cancer registry data. *Surgical Oncology.* 2005; 13:175-179.

(92) Brenner H, Hakulinen T. Reduction in selective under-ascertainment bias in population-based estimates of cancer patient survival by age adjustment. *European Journal of Cancer.* 2005; 41:1788-1793.

(93) Jack RH, Davies EA, Møller H. Testis and prostate cancer incidence in ethnic groups in South East England. *International Journal of Andrology.* 2007; 30:215-221.

(94) Moran A, O'Hara C. UK database for teenagers and young adults with cancer. Shack L, editor. 2008. 9-6-2008.

(95) Wood AM, White IR, Hillsdon M, Carpenter J. Comparison of imputation and modelling methods in the analysis of physical activity trial with missing outcomes. *International Journal of Epidemiology.* 2005; 34:89-99.

(96) van Burren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Statistics in Medicine.* 1999; 18:681-694.

(97) Royston P. Multiple imputation of missing values. *Stata Journal.* 2004; 4:227-241.

(98) Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Statistical Methods in Medical Research.* 2007; 16:199-218.

(99) Carpenter J, Kenward MG, White IR. Sensitivity analysis after multiple imputation under missing at random: a weighting approach. *Statistical Methods in Medical Research.* 2007; 16:259-275.

(100) Brewster DH, Crichton J, Muir CS. How accurate are Scottish cancer registration data? *British Journal of Cancer.* 1994; 70:954-959.

(101) Brewster DH, Stockton D, Harvey J, Mackay M. Reliability of cancer registration data in Scotland, 1997. *European Journal of Cancer.* 2002; 38:414-417.

(102) Wrigley H, Roderick P, George S, Smith J, Mullee M, Goddard J. Inequalities in survival from colorectal cancer: a comparison of the impact of deprivation, treatment and host factors on observed and cause specific survival. *Journal of Epidemiology and Community Health.* 2005; 57:301-309.

(103) Measuring deprivation subgroup. *Deprivation and urban rural measurements in ISD.* Edinburgh: ISD, 2004.