Intervention-generated inequalities in lung cancer care

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Abstract

Lung cancer survival is poorer in more socio-economically deprived patient groups. It has been suggested that socio-economic inequalities in receipt of, and time to, treatment may contribute to inequalities in cancer outcome. Unintended variations in outcome that result from the way that interventions are organised and delivered have been described as intervention-generated inequalities.

The aim of this thesis was to determine if there are socio-economic inequalities in lung cancer care and, if so, to identify where on the pathway of care these inequalities might occur: looking at receipt of treatment; referral, diagnostic and treatment time intervals; and survival.

A systematic review and meta-analysis was conducted in order to examine the published evidence for socio-economic inequalities in lung cancer treatment. A secondary analysis of cancer registry data for 65,210 patients diagnosed between 1999-2010 with a primary diagnosis of lung cancer [ICD10 C33 and C34], linked to Hospital Episode Statistics and lung cancer audit data, was conducted. Logistic regression was used to examine the likelihood of receipt of treatment; of receiving timely referral, diagnosis and treatment within guidelines; and of being alive two years after diagnosis, by socio-economic position [SEP]. Cox regression was used to assess the likelihood of early referral, diagnosis and treatment and hazard of death, by SEP.

Socio-economic inequalities in receipt of lung cancer surgery and chemotherapy, but not radiotherapy, were found in the systematic review and meta-analysis, and in the linked-data analysis. Socio-economic inequalities in the GP referral to first hospital appointment time interval were identified. Socio-economic inequalities in survival from lung cancer were statistically explained by socio-economic inequalities in receipt of treatment, but not by inequalities in timeliness of referral and treatment, in this cohort. However high levels of missing stage, performance status and co-morbidity data were a limitation.

Research into the unexplained variance in treatment rates is required in order to develop interventions that address socio-economic inequalities in receipt of treatment and reduce socio-economic inequalities in survival.

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Publications from the thesis

Peer reviewed papers

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Editorials

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Abstracts

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List of abbreviations

CCM score	Charlson co-morbidity score
CI	Confidence interval
FHA	First hospital appointment
HES	Hospital Episode Statistics
HR	Hazard ratio
ICD	International Classification of Disease
IGIs	Intervention-generated inequalities
LUCADA	Lung cancer audit
MDT	Multi-disciplinary team
NAEDI	National Awareness and Early Diagnosis Initiative
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NSCLC	Non-small cell lung cancer
NYCRIS	Northern and Yorkshire Cancer Registry and Information Service
OR	Odds ratio
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PS	Performance status
SCLC	Small cell lung cancer
SEER	National Cancer Institute's Surveillance , Epidemiology and End Results database
SEP	Socio-economic position
UHCS	Universal healthcare system

Chapter 1. Introduction

The aim of this thesis is to explore the evidence for intervention-generated inequalities (IGIs) in lung cancer treatment: to examine the published evidence for socio-economic inequalities in lung cancer treatment; to use routine secondary data to determine if there are inequalities in lung cancer care, and to identify where on the pathway of care these inequalities might occur – looking at inequalities in receipt of treatment, time to treatment, and survival.

Chapter 1 presents a general introduction to the thesis. Chapter 2 reviews the literature on IGIs, and chapters 3, 4 and 5 examine the evidence for IGIs and cancer, whilst chapter 6 details the aims and objectives. Chapter 7 examines the published evidence for socio-economic inequalities in lung cancer treatment using a systematic review and meta-analysis, and chapters 8-12 present the research methods and results from the secondary data analysis. Chapter 8 details the methods and chapter 9 presents descriptive analyses, before going on to explore socio-economic inequalities in lung cancer treatment [chapter 10], referral, diagnostic and treatment intervals [chapter 11] and survival [chapter 12]. An overall discussion of the thesis findings is then presented in chapter 13.

The general background to the topic will now be examined.

1.1 Health inequalities

Despite improvements in living standards, introduction of the welfare state and free NHS care for all, socio-economic differentials in health are still observed in the UK (1). Health inequalities can be defined as differences in health outcomes between groups within populations [or between populations]. Although health inequalities due to biological differences are inevitable, it is recognised that inequitable differences in health also exist, which are unfair and potentially avoidable (2, 3). Health inequalities have been observed using a number of different measures of socio-economic position [SEP] (2, 4).

1.1.1 *Socio-economic position*

Socio-economic position is a construct used to measure the social and economic factors that influence the position of an individual or group within society (5), using area-based, household, and individual measures of deprivation, poverty, wealth, income and education (6).

There are advantages and disadvantages to using each of these markers of SEP, which need to be taken into account when examining health inequality. Education is easy to measure, applicable to all and is generally stable over adulthood. However, it is strongly influenced by parental and societal characteristics and there are cohort effects. It is a less sensitive measure of SEP than income, but income is often poorly reported and excludes non-working groups (5). Household rather than individual income can often be a better measure of SEP for women. Poverty is a subjective measure and is determined by societal norms. Using a neighbourhood measure of SEP means there is danger of ecological fallacy but it can apply to all ages and both sexes (6).

1.2 Intervention-generated inequalities

Intervention-generated inequalities have been described as health inequalities that result from the way that health interventions are organised and delivered (7) so that, although overall health may improve as the result of an intervention, differences in access to the intervention, differential uptake, delays in uptake, differential compliance with, or effectiveness of, an intervention might result in inequalities in outcome.

Inequalities are likely to occur at many different stages of intervention pathways and act in a cumulative way. It is also likely that intervention-generated inequalities contribute to overall socio-economic inequalities in morbidity and mortality, although this has not been conclusively demonstrated (7).

1.3 Cancer

Cancer is a term used for a number of diseases in which normal cells change so that they grow in an uncontrolled way and are able to invade other tissues. The uncontrolled growth causes a tumour to form. Cancer cells can spread to other parts

of the body through the blood and lymph systems. There are more than 200 different types of cancer and most are named for the organ or type of cell in which they start.

Most cancers are carcinomas, which are cancers of the epithelial cells [tissue that covers and lines the body]. Carcinomas make up about 85% of cancers. There are different types of epithelial cells and these can develop into different subtypes of carcinoma, including adenocarcinoma and squamous cell carcinoma.

Staging is a way of describing the size of a cancer and how far it has grown and spread to another part of the body, whereas the grade of cancer describes how similar the cancer cell is to a normal cell. Staging is important in determining treatment. For localised cancer, surgery or radiotherapy could be curative. If a cancer has spread, then systemic treatments such as chemotherapy or hormone therapy [that circulate throughout the bloodstream] may also be required.

Cancer patients often suffer from a number of concurrent health conditions which are termed co-morbidities. Performance status [PS] is a measure of general well-being and ability to care for oneself that is assessed by the care team. Both these variables may be used to help determine the most suitable cancer treatment when patients are assessed. More details on these variables will be presented in chapter 8.

1.3.1 *Cancer incidence, mortality and inequality*

Breast, lung, colorectal and prostate cancer are the top four cancers for incidence and mortality in the UK and together account for over 54% of UK cancer incidence (8) and 47% of cancer mortality (9). Lung cancer is the leading cause of cancer death accounting for 22% of cancer mortality followed by colorectal cancer at 10% (9).

Inequalities in cancer incidence are found for a number of common cancers (8). Higher cancer incidence within more deprived populations is associated with higher rates of smoking and alcohol consumption, unhealthy diet and lack of exercise, all of which contribute to a higher risk of cancer (8).

A statistically significant association between higher colorectal cancer incidence and socio-economic deprivation has been reported for men in England and Wales (10). However, this association is not always seen worldwide. A review reported that those

with lower SEP had higher colorectal cancer incidence compared to higher SEP groups in the USA and Canada, but that the reverse was true in Europe, where those with lower SEP had lower risk (11). However, no UK studies were included and a number of European studies did show an increased risk with lower SEP. Conversely higher incidence in less deprived populations is found for breast cancer and malignant melanoma in England (12).

Around 63% of cancers are diagnosed in people aged 65 and over, and more than a third are diagnosed in the elderly [aged 75 and over].

Survival varies markedly by cancer type. Whereas around 50% of those diagnosed with colorectal cancer and 80% with breast cancer can expect to still be alive five years after diagnosis only around 6% of those with lung cancer can (9). Whilst survival rates have greatly improved for most cancers in recent years this improvement has not been seen for lung cancer.

1.3.2 *Lung cancer*

Lung cancer is the most common incident cancer, worldwide. In the USA and the UK it is the second most incident cancer after breast cancer (8, 13) [and the second most common for men after prostate cancer and for women after breast cancer], as well as the most common cause of cancer mortality (9, 13). Survival differs internationally. In the UK less than 10% of those diagnosed with lung cancer survive for 5 years (9, 14), with higher survival rates found in Nordic countries (14, 15), the USA (13, 15), Australia and Canada (14).

A strong socio-economic gradient for lung cancer incidence is seen in the UK, with rates 2-3 times higher in the more deprived (8). Higher incidence and mortality is found in the north of England compared to the rest of the UK also (8), and the incident deprivation gap is wider (12). A systematic review and meta-analysis found that, worldwide, lung cancer incidence was associated with low education and low SEP [both occupational and income-based] and remained so in subgroup analyses adjusted for smoking (16). Smoking has been strongly associated with incidence of small cell lung cancer, and also squamous cell non-small cell lung cancer but less so with adenocarcinoma tumour type. There is some suggestion that past smoking behaviour

may account for much of the socio-economic inequalities in risk of lung cancer (17), but not all, as an SEP gradient in incidence remains when smoking status is taken into account (16).

Lung cancers are classified into small cell [SCLC] and non-small cell [NSCLC] cancers, with NSCLC accounting for 80% of lung cancers. NSCLC can be further divided into squamous cell carcinomas, adenocarcinomas and large cell carcinomas (18). Studies have found different proportions of NSCLC subtypes.

Squamous cell carcinoma has historically been strongly associated with smoking but, with the introduction of lower tar and nicotine cigarettes, the incidence of this subtype is falling (19). Adenocarcinomas are a morphologically heterogeneous group and although they are also associated with smoking [generally of low-tar filtered cigarettes (17)] they are also found in those who have never smoked, particularly in women (19). Large cell carcinomas are the least common subtype and are often misclassified (19).

SCLC are thought to account for around 20% of lung cancers although this proportion has been reported to be falling in more recent years (20). SCLC is also strongly associated with smoking and the decrease in incidence of SCLC over time, similarly to the squamous subtype for NSCLC, may be related to the reduced prevalence of smoking and type of cigarettes smoked (20).

1.3.2.1 *Lung cancer staging*

Lung cancer stage is determined using the 'Tumour, Node, Metastasis' [TNM] staging system (21). The TNM staging system describes the size of the primary tumour, whether the cancer has spread to the lymph nodes and whether the cancer has spread to a different part of the body [metastasised]. 'T' refers to the size of the cancer, going from 1 [small] to 4 [large]. The letters A, B or C can be used to further divide the number categories. 'N' refers to whether the cancer has spread to the lymph nodes - from 0 [no positive nodes] to 3 [many positive nodes]. 'M' refers to whether the cancer has spread to another part of the body - either 0 [the cancer has not spread] or 1 [the cancer has spread] (21).

In stage 1 lung cancer the cancer is small [1A: up to 3cm, 1B: 3-5cm] and localised, and has not spread to the lymph nodes (21). In stage 2A, the cancer is between 5-7cm and

has not spread to the lymph nodes. Stage 2B includes cancers that are 5-7cm and have spread to the lymph nodes close to the affected lung; cancers larger than 7cm but with no lymph node spread or that have spread to the chest wall, diaphragm, phrenic nerve, layers covering the heart, or bronchus; cancers larger than 7cm where part of the lung has collapsed; or cancers of any size where there is more than one tumour in the same lobe of the lung (21). In stage 3A lung cancer the cancer is larger than 7cm and has spread to the lymph nodes close to the affected lung; or any size but spread to the heart, trachea, oesophagus, nerve, spinal bone or blood vessel. In stage 3B the cancer is in the mediastinum lymph nodes and has spread to the chest wall, diaphragm, heart, trachea, oesophagus or major blood vessels. In stage 4 the cancer is in both lungs; or has spread to another part of the body; or cancer cells are in a fluid collection around the heart or lungs (21).

1.3.2.2 *Lung cancer treatment*

National Institute for Health and Clinical Excellence [NICE] guidelines [2005] recommend radical surgery [pneumonectomy or lobectomy] for stage I or II NSCLC. Chemotherapy and radical radiotherapy are recommended for stage IIIa, with chemotherapy for stage IIIb and stage IV lung cancer patients with good performance status. Radiotherapy may be given as a palliative option for stage IV patients with poor performance status (18). Figure 1.1 summarises these NICE recommendations. Updated guidelines from 2011 now recommend radical radiotherapy for stage I-III NSCLC patients (22). Chemotherapy and radiotherapy were the treatments of choice for SCLC but surgery is now recommended for early stage SCLC (22). Intervention with surgery, chemotherapy or radiotherapy has been shown to improve survival (18).

Fitness for treatment is assessed using the following NICE guidance pathway [Fig 1.2] (22).The type of cancer treatment given is generally determined by cancer stage, but also by the performance status of the patient and the number and type of co-morbidities suffered. Lung cancer sufferers tend to be old [age 70+] and to be smokers so that high rates of chronic obstructive pulmonary disease [COPD] and ischaemic heart disease are common (23), often making radical surgery unsuitable for these patients.

Figure 1.1.Treatment matrix for NSCLC (2005 recommendations)[18]

	Stage I	Stage II	Stage IIIA	Stage IIIB	Stage IV, PS 0–1	Stage IV, PS 2	Stage IV, PS > 2
Surgery							
Radiotherapy followed by surgery							
Surgery followed by radiotherapy							
Preoperative chemotherapy and surgery	a	a	a				
Surgery followed by chemotherapy							
Surgery then chemo- and radiotherapy		a	a				
Radical radiotherapy							
Chemotherapy and radical radiotherapy				b			
Chemotherapy						a	
Symptomatic treatment, including palliative radiotherapy							

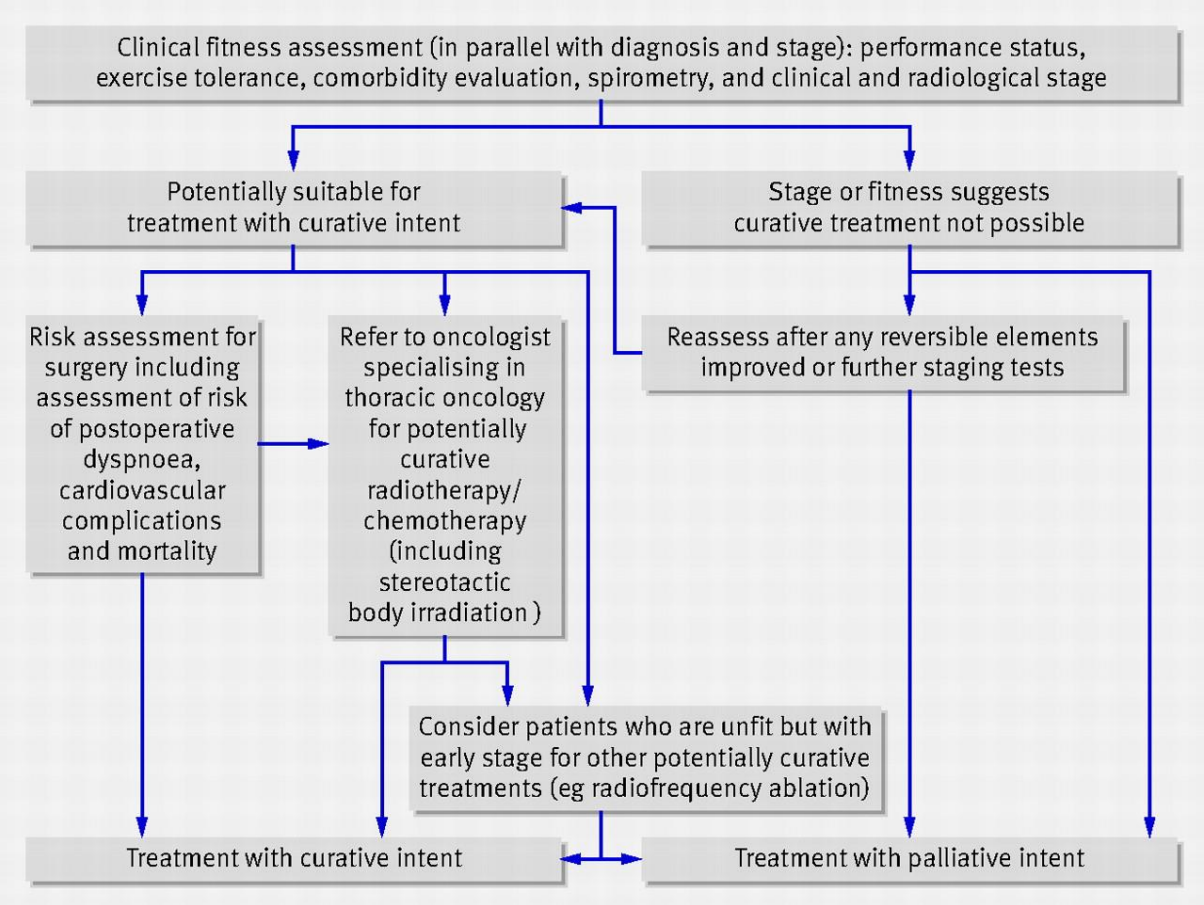
Key:

First choice for eligible patients	Suitable for some patients (see recommendations)	Not recommended

[a] Except within a clinical trial.

[b] May be first choice of treatment for patients with good performance status and localised disease that can be safely encompassed in a radical radiotherapy treatment volume.

Figure 1.2. NICE guidelines (2011) Fitness assessment clinical pathway: lung cancer [22]



1.4 Cancer inequalities

Inequalities in cancer care within the UK have been noted and the NHS Cancer Plan in 2000 pledged to reduce cancer mortality, reduce delay in diagnosis and treatment and increase survival whilst acting to reduce inequalities (24). More recently the National Cancer Equality Initiative has been set up to address some of these issues (10) as, although the incidence and survival of many common cancers varies with SEP (8, 25, 26), little is known about inequalities in receipt of, and time to, treatment and how these might contribute to inequalities in outcome. However, in a 2006 review that summarised a decade of research on the association between SEP and cancer survival, it was suggested that socio-economic differences in 'access to optimal treatment' (26) might at least partially explain survival differences.

Lung cancer is the leading cause of cancer death within the UK [with mortality rates higher in the North of England and Scotland than in the rest of the UK] and it has been suggested that reducing the socio-economic gradient in survival could prevent many thousands of avoidable cancer deaths (9). It has been estimated that over 1300 deaths could be avoided annually in England and Wales if the survival rate in the more deprived socio-economic groups were similar to that of the most affluent (27). However, in order to do this it is necessary to identify those factors that may contribute to outcome inequalities. Access to treatment may be one such factor. For example, resection rates in the north-east are lower than those for England as a whole (28) and this might contribute to the poorer survival observed locally.

Socio-economic inequalities in receipt of cancer care have been found in individual studies for a number of cancers and assessed in a review for colorectal cancer (11) but there has been no systematic review of the evidence to demonstrate if such inequalities in receipt of treatment exist for lung cancer.

A previous study conducted in the Institute of Health and Society [IHS] at Newcastle University explored socio-economic inequalities in the delivery of pancreatic cancer care, using Northern and Yorkshire Cancer Registry and Information Service [NYCRIS] data, and found evidence of socio-economic differences in time from GP referral to first hospital appointment and in receipt of treatment (29). This study will build on these findings, using the intervention-generated inequalities framework to explore inequalities in cancer care for lung cancer, whilst also undertaking a systematic review of the evidence into inequalities in receipt of treatment.

The next chapter will describe the concept of, and explore the evidence for, Intervention-generated inequalities.

Chapter 2. Literature review – Intervention-generated inequalities

This chapter will define intervention-generated inequalities [IGIs], review the evidence for IGIs in the literature, as well as exploring the potential reasons for inequalities in receipt of healthcare and public health interventions.

2.1 IGIs - Background and framework

Health inequalities can be found across a number of dimensions including: place of residence [urban/rural], race/ethnicity, occupation, gender, religion, education, socio-economic position [SEP] and social capital, which have been given the acronym PROGRESS (30). If other dimensions such as age, disability and sexual orientation are included then this the term PROGRESS–Plus is applied (30).

The intervention-generated inequalities [IGI] concept was developed by White et al [2009], in order to produce a framework for a more evidence-based theory and model of intervention inequality (7), as previous equity 'laws' and hypotheses had been used in a fairly loose and interpretive way throughout the equity literature. Intervention-generated inequalities have been described as health inequalities that result from the way that health interventions are organised and delivered (7). Although overall health may improve as the result of an intervention, differences in access to the intervention; differential uptake; delays in uptake; differential compliance with; or effectiveness of; an intervention, may result in inequalities in outcome. There may also be inequalities in timeliness of the offer of the intervention and to whom it is offered.

The IGI framework expands on previous equity hypotheses that have attempted to describe variations in the provision and uptake of interventions. The 'Inverse Care Law' [ICL] first described by Tudor-Hart in 1971 stated that "the availability of good quality health care is inversely related to need in the population served" (31). The ICL has been cited in a number of studies concerning access to primary care, healthcare utilisation (32), GP prescription practices and satisfaction with care (7), but it only looks at provision of care in relation to need. Whilst SEP can be seen as a proxy marker for 'need' [with the assumption that those of lower SEP have more need of care] the ICL does not consider intervention effectiveness. The focus is on the organisation and delivery of standardised care whereas, in order to address inequalities, it might be

more important to consider different types of care and the context in which care is delivered.

The ‘inverse Prevention Law’ suggests that a similar socio-economic gradient also exists in disease prevention but this was an idea that appeared within the Acheson Report in 1999 (33) without any empirical evidence to back up this claim (7).

The ‘inverse equity hypothesis’ proposed that public health interventions initially widen socio-economic inequalities due to preferential uptake by more advantaged groups before the less advantaged follow suit, eventually improving health overall (34). Although evidence-based using child health studies from Brazil, it was developed for low-income countries but has been used as a framework elsewhere, for example in looking at uptake of new cancer treatments in the UK (35). The hypothesis builds on the ‘diffusion of innovation’ theory (34) and makes the assumption that all interventions are appropriate for everyone and so could be seen to ascribe blame to those who are slower to ‘innovate’ and uptake. It does not consider that some interventions may not be suitable for all and so will never diffuse downwards.

The Tugwell ‘staircase’ model suggests that inequalities at different stages of an intervention may combine multiplicatively in order to reduce intervention effectiveness in the more deprived (36). Lower access to the intervention [including awareness or coverage], inequalities in diagnosis [screening or targeting], provider compliance, and consumer adherence in more deprived populations means that this staircase effect increases the relative equity-effectiveness gap between rich and poor (36).

None of the above equity laws and models examines how interventions can be designed to reduce inequality. It needs to be considered whether it is enough to provide a standard level of care to all or whether targeted interventions tailored to specific groups might be more effective. Therefore, in order to expand the previous equity laws into a framework to address intervention-generated inequalities it is necessary to examine all the possible stages where inequalities may be introduced, determine which aspects of an intervention may lead to inequalities, and consider ways in which these can be reduced or eliminated.

2.2 Differential receipt of healthcare

A number of reasons have been suggested for differential receipt of healthcare, ascribed to both patient and system factors (37). However, when considering inequalities in access to, and receipt of, care, it is important to first take into account the type of healthcare system.

2.2.1 *Healthcare system*

In the UK, the National Health Service [NHS] is free at the point of use. Access to care is therefore, in theory, equally available to all UK citizens who require it. Other countries, including the United States (US), have a non-universal health care system, where access to healthcare is determined by insurance status. Citizens [generally those who are in work] can purchase private insurance, and social insurance programmes - Medicare [for those aged over 65] and Medicaid [for certain categories of people who are on a low income or are disabled] - are also available (38).

There is a wealth of evidence to show that lack of a universal healthcare system can result in disparities in access to treatment (38, 39). In 2002, 17% of Americans were uninsured (38), and there is considerable inequity, by income and race, in insurance coverage (38).

2.2.2 *Patient and practitioner factors*

Eligibility for healthcare has been described as 'candidacy' where it 'is jointly negotiated between individuals and health services' (40). How individuals identify themselves as requiring medical attention may depend on their health expectations and how they manage health and recognise symptoms. They must then be able to navigate the system and access care (40). Socio-economic barriers to uptake may be financial, psychological and educational. For example, specialist care centres may be geographically distant and it may be more difficult to access services for those who cannot afford childcare, are unable take time off from work or do not have access to a car (37). Lower SEP patients report struggling to navigate a complicated appointments system in order to access GP care (41). It may be easier to use emergency services that do not involve making an appointment or require a referral, but this could result in

patients delaying presenting until symptoms become more severe and when they are at a more advanced stage of the disease pathway.

A realist review [a review method that falls between a systematic and narrative review] found evidence that, as middle-class service users tend to be more vocal, this may influence their interaction with health services and the likelihood of referral and receipt of treatment, as well as determining the type and quality of information provided to them by health professionals (42).

Differences in communication patterns between health professionals and patients by SEP have been described that may influence the treatment prescribed (37). The patient must be able to articulate the problem and request help and the ability to do so may affect the likelihood of referral (40). Healthcare professionals may make treatment decisions based on which patients they consider likely to do well, using factors such as age, weight and co-morbidity. There is some evidence that those who are in work are more likely to be referred (40) and these subjective judgements may disadvantage those of lower SEP. Adherence to treatment protocols has also been shown to differ by SEP, as has treatment refusal (40), which may be related to understanding of risk.

2.2.3 *Health literacy*

The ability to interpret symptoms, understand risk and effectively navigate the healthcare system can be included under the general heading of health literacy. Health literacy has been defined as 'the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions' (43). Health literacy has been proposed as a major determinant of population health and health inequalities, although Nutbeam [2008] suggests that 'the corrosive impact' that poor literacy may have on health remains well hidden (43). It is likely that poorer health literacy plays a role in the higher prevalence of adverse health behaviours that result in higher disease incidence in more deprived SEP populations.

Much of the early research examining health literacy and healthcare interactions has been conducted in the US. In a recent systematic review the authors found evidence of an association between poor health literacy and reduced ability to manage chronic conditions and take medication appropriately, lower use of mammography screening and flu vaccine uptake, higher rates of hospital admission and emergency admissions, and poorer health outcomes in the elderly, but the evidence for a relationship between health literacy and access to care was judged as insufficient (44). It was also suggested that lower health literacy may partially explain racial disparities in some health outcomes (44). SEP was not considered but it seems feasible that health literacy may also play some role in disparities in health outcome by SEP.

A recent UK study found that low functional health literacy [the ability to apply basic reading skills in a health context] was associated with higher mortality (45). There is some evidence to suggest that low health literacy is found at higher rates amongst low SEP groups, as well as in older patients and ethnic minorities (46) although much of this research has been carried out by UK consumer groups rather than in academia. A recent qualitative UK study found that patients from GP practices in low SEP areas did appear to have lower health literacy than those from higher SEP areas and, as well as a difference in health knowledge, there was also a difference in role expectation (41). Patients' willingness to actively participate in the consultation depended on their cultural and normative expectations of the doctor and patient role. Lower SEP patients felt less able to question the doctor and often felt it was not their place to do so (41). Patients of higher SEP are more likely to state a preference for involvement in medical decision making [as are women and younger patients] (47) but in order to make an informed decision patients must be able to understand the information provided.

Poor understanding of health information is not a minor problem as studies have estimated that over 50% of the UK adult population struggle to understand narrative health information, and this rises to over 70% when numbers are included in the information and where basic numeracy skills are required (46). Patients often do not understand complex medical terminology and this problem is compounded by the fact that health care professionals in turn do not recognise the extent of the problem and tend to over-estimate their patients' understanding (48). Health literacy can be context-specific and, within a healthcare environment, the use of unfamiliar

vocabulary and terminology can be stressful and alienating. It is possible that health literacy may influence patient choice. If patients have poor capacity to process and understand basic health information then they are less able to make appropriate health decisions.

It has been suggested that the current UK government emphasis on patient involvement in health decision making may increase health inequalities (46), as only those with good health literacy are fully able to participate in effective shared decision making. This might be seen as a further example of an intervention-generated inequality.

2.3 IGIs – examples from the literature

I will now consider what, if any, evidence exists for the occurrence of intervention-generated inequalities, the types of interventions that are likely to produce IGIs and those which may reduce inequalities.

2.3.1 *Review evidence*

Two early systematic reviews examined interventions to reduce health inequalities (49, 50), looking at interventions to reduce cancer incidence [screening, smoking cessation] and heart disease, accident prevention, reduce risky sexual health behaviour and unwanted pregnancy, and improve accessibility of healthcare. Arblaster et al (1996) found that successful interventions for reducing health inequalities used systematic and intensive health-care delivery approaches, improved access and used prompts to encourage service use, designed tailored interventions specifically for the target population and used peers to help deliver the intervention (49). However, they also found that not all these features were necessary to reduce inequalities but, conversely, that these characteristics alone were not enough to ensure equality. The scope of the review was quite narrow as it considered only interventions that could be carried out by a health service, and the authors were only able to conduct a narrative synthesis of the evidence as the settings, populations and outcomes were so diverse.

A similar review conducted in the same year was wider in scope but included some of the same interventions and studies. Gepkens et al [1996] found that structural interventions were most effective. Interventions involving health education only

seemed to be effective in lower SEP groups when supplemented by personal support or structural measures (50). However, the majority of the interventions examined aimed to increase knowledge or change behaviour rather than having a specific health outcome. And, again, the diversity of the interventions meant that meta-analysis was not possible.

A 2008 systematic review looked at social inequalities [assessed using PROGRESS criteria] in tobacco control interventions (51) and identified multiple gaps in the evidence base. There was some evidence that workplace restrictions on smoking may be more effective in the more affluent (51). However, much of the evidence was from the USA and so may not be relevant in other countries. There was little evidence on differential effects by SEP, sex or ethnicity and, in order to address this, the authors suggested that in population-level studies pre-planned subgroup analyses should be carried out to examine inequalities (51).

A short systematic review of reviews published in 2012 used a limited search strategy but employed systematic screening of papers to identify evidence for the types of interventions that might generate inequalities (52). However, this 'rapid review' did not look at interventions involving access to healthcare. The authors again found that data was lacking but, the 12 reviews that they were able to include, there was some evidence that interventions that involved structural change, pricing and the provision of resources appeared to reduce socio-economic health inequalities, whereas those that merely provided information, such as media campaigns, increased inequalities (52). That is, more 'upstream' social, fiscal or policy-level legislative interventions appeared more equitable than those that relied on education or information-provision to engender voluntary behaviour change. Further evidence has been found to support this theory, as is described below.

2.3.1.1 *Interventions that reduce inequalities*

A health voucher scheme in Bangladesh found that the introduction of vouchers for maternal health care reduced socio-economic inequalities in service utilisation and, contrary to the inverse equity hypothesis, better early uptake was seen in the poorer rather than more affluent women (53). Other financially-related interventions have also been shown to reduce inequalities; for example, tobacco price increases are more

likely to reduce smoking in lower-income adults and those in manual occupations whereas smoking cessation services are less effective in these groups (51).

Legislative changes may also favour the more deprived, as seen in water fluoridation (54), and motorbike helmet use (55). The introduction of a mandatory motorcycle helmet law in Taiwan reduced regional socio-economic inequality in mortality from road traffic accidents and this was most marked for men aged under 25 (55). However, inequalities began to increase again 5 years after introduction of the law, so it may depend on how strictly a law is enforced as to whether people continue to comply equitably. Rear-seatbelt use in the UK is mandatory but a socio-economic gradient in compliance is found (56).

Although not all of these studies may be directly relevant to the UK, they provide examples of the principle that the equitable effectiveness of an intervention may depend on the level of control and voluntary engagement an individual has.

2.3.1.2 *Interventions that increase inequalities*

Inequalities in uptake of population-based non-mandatory public health interventions such as cancer screening and immunisation, were identified in a narrative review of evidence for IGIs (7). A UK intervention designed to improve uptake of childhood vaccinations improved overall uptake but widened socio-economic inequalities in uptake (57).

A study that examined smoking inequalities in Sweden and Denmark found that, in Sweden, where the government had implemented an active, population-based anti-smoking campaign, overall levels of smoking were lower but inequalities were higher, with better educated individuals having responded best to the strategy, compared to Denmark (58), where less forceful anti-tobacco policies had been implemented.

2.3.2 *Gaps in the evidence base*

It does appear that there is a lack of systematic evidence on the type of interventions that may result in inequalities in health, as well as in where on the intervention pathway that intervention-generated inequalities may be occurring.

Equity assessments are rarely conducted as part of systematic reviews and, in a random sampling, only one in 95 Cochrane Reviews examined outcome effects across PROGRESS factors (30). In an, as yet unpublished, review on the variations in effectiveness of obesity treatment and prevention interventions by SEP it was noted that the majority of papers recovered did not detail outcome by SEP in the abstract, even if it was detailed in the main text [Martin White, *personal communication*]. A 2013 pilot review examining systematic reviews of physical activity interventions found that only 26% of these were prospectively designed to examine inequalities (59).

Comparing the effects of interventions in different populations often requires that studies carry out sub-group analyses. However studies may not be suitably powered to allow detection of sub-group differences, and if post-hoc subgroup analyses are carried out, without suitable consideration of plausibility in relation to inequity theory, then researchers may find themselves accused of 'data-dredging' by disapproving statisticians (60).

In a methodological study of equity assessment in systematic reviews, of 224 systematic reviews indexed on Medline in one month, only 13% of these examined were found to have conducted subgroup analysis by PROGRESS-plus factors (61). It is often difficult, therefore, to assess the effects of interventions on health equity as few studies report their results in this way. But it is important to do so, as unequal benefits across socio-economic groupings are likely to contribute to decreased health equity (30) which can be considered as unethical and unfair, as well as sub-optimally cost-effective. There are also implications for generalisability, as, if only the more affluent take up an intervention, the data may not be applicable at a population-level (62). However, this scarcity of evidence means that the contribution of intervention-generated inequalities to overall socio-economic inequalities in morbidity and mortality is still unclear.

2.4 Summary

Although the evidence base for intervention-generated inequalities remains limited, it does appear that financial and legislative interventions, and those which are specifically targeted at particular groups, are less likely to introduce intervention-generated inequalities than those that rely on voluntary uptake or that provide a 'one

size fits all' solution for prevention and treatment. However, the patient and system factors that influence access to, and uptake of, healthcare and public health interventions are also not well evidenced and need to be determined in order to eliminate IGIs.

Chapters 3-5 will examine the evidence for IGIs in cancer care.

Chapter 3. Intervention-generated inequalities in cancer care: receipt of treatment

As described in chapter 2, the evidence base for IGIs is somewhat limited. I will now look at the evidence for IGIs specifically in relation to receipt of cancer treatment, and why these might be found.

3.1 Introduction

Previous work looking at inequality in pancreatic cancer care, using NYCRIS data (29), found a significant socio-economic trend in receipt of any treatment, with the odds of receiving treatment increasing from the most to the least deprived quintile when age, sex and co-morbidity were taken into account. This trend was also seen for receipt of any radical surgery but not for adjuvant chemotherapy. It was also seen for any palliative oncology treatment, any palliative chemotherapy, but not radiotherapy or hormone therapy. Differences in access to treatment might be partially explained by differences in stage at presentation, but unfortunately staging information was not available.

Time from GP referral to hospital investigation was significantly shorter in the less socio-economically deprived groups compared to the most deprived [and for older compared to younger patients], but this trend was not seen when looking at time from first hospital appointment to diagnosis, or time from diagnosis to any therapy or treatment [apart from in time to palliative radiotherapy] (29). Therefore, there is some evidence of socio-economically patterned delay in time from referral to first hospital appointment for pancreatic cancer.

Building on this first attempt to examine intervention-generated inequalities in cancer care, looking at pancreatic cancer, I will now use the intervention-generated inequalities framework to assess where on the pathway of cancer care inequalities might occur and why they might occur. The evidence for inequalities in receipt of treatment in all cancers is considered in this chapter, including the evidence specifically relating to lung cancer. Inequalities in time intervals on the care pathway are examined in chapter 4 and inequalities in survival in chapter 5. Socio-economic

inequalities in receipt of treatment and in time to presentation, referral, diagnosis and treatment may all contribute to inequalities in survival.

3.2 Inequalities in receipt of treatment

Existing published evidence for inequalities in receipt of treatment for cancer and why these might occur will be examined here.

3.2.1 *Why might socio-economic inequalities in receipt of treatment be found?*

Patient, tumour and system factors may all be relevant for differential receipt of cancer care.

Patients may delay in accessing healthcare, choose not to undergo active cancer treatment or to comply with treatment protocols for a number of reasons, often involving a complex mixture of financial, psychological, cultural, practical and educational factors (37), as previously discussed. Low SEP has been associated with colorectal cancer treatment refusal (63) and this may be related to poor health literacy. However, a Scottish study of 882 lung cancer patients found no association between refusal of treatment and SEP (64).

Tumour factors such as stage may also be relevant. Later-stage patients are less likely to receive surgery and there is some evidence for a socio-economic gradient in stage at presentation for some cancers (65-67) but not all (68).

The use of co-morbidity and PS to determine suitability for treatment may offer a partial explanation for socio-economic and age-related inequalities in treatment, as the number of co-morbidities and PS vary by SEP (69) and age (70). Higher co-morbidity has been associated with older age, female sex and lower SEP in lung cancer patients (71) and might reduce the likelihood of surgery for these patients. However, another study found that chronological age rather than performance status or the number of co-morbidities determined whether elderly patients with lung cancer were actively treated. Many doctors adopted a 'nihilistic approach' to treatment and guidelines were not followed for older patients (72). SEP was not considered in this study, but differences in doctor-patient interactions between higher and lower socio-economic groups (73) have also been suggested as a reason for different socio-

economic cancer treatment patterns where 'unrecognised personal biases and beliefs may affect recommendations of cancer treatment' (37).

Doctor-patient communication has been shown to differ by race in the US. Black lung cancer patients and those in 'racially discordant interactions' received less information and participated less actively in the consultations (74). It is possible that similar discrepancies by SEP are also found.

In the English National Cancer Patient Experience Survey for 2011/12, differences in responses from patients were found by SEP. More deprived patients reported that their views were taken into account when the clinical team discussed which treatment they should have, and possible side effects of treatment were explained in a way they could understand (75). However, they also reported delays in diagnosis and that they were less likely to receive understandable information or explanations (75).

Patients in the least deprived quintile were more likely to report a better patient experience than the most deprived, for a number of questions that could relate to their level of health literacy. They reported 'being given the right amount of information about their condition and treatment, given understandable answers to questions by ward nurses all or most of the time, given easy to understand information about the type of cancer they had and given easy to understand written information about tests beforehand' (75). These survey results may suggest that there are, indeed, differences in the way that doctors communicate, or that differences in health literacy between higher and lower SEP groups determine how well understood the information given is.

3.2.2 *Evidence for socio-economic inequalities in receipt of treatment*

Socio-economic inequalities in receipt of treatment have been found for some cancers, with the majority of evidence from studies looking at colorectal cancer.

In a 1998 UK study utilising Hospital Episode Statistics [HES] data from patients admitted between 1992 and 1995 in south-east England, and using Townsend scores as an area-based measure of SEP, patients from less affluent areas were less likely to receive surgery for lung and breast cancer but not for colorectal cancer (76), in a multivariable analysis adjusted for age and sex. This was a well-conducted study but a

number of potentially important confounders such as stage were not included. In a similar study in 2010 looking at UK-wide HES data from 1999-2006, patients from deprived areas were less likely to receive optimal surgical treatment for breast, lung and also rectal cancer, taking into account age, sex and year of admission, but again not stage (77). Inequalities in stage at presentation might account for some of these socio-economic differences.

In a UK paper that was primarily concerned with examining geographical access to cancer treatment, the authors noted that surgery was less likely for deprived patients compared to the more affluent using data for breast, colon, rectum, lung, ovary and prostate cancer diagnosed between 1994 and 2002, also taking into account age, sex and travel time to hospital, and stage for all except for lung or prostate, as staging information was not well recorded for these cancers (78). Deprived patients were also less likely to receive chemotherapy [except for breast cancer] and less likely to receive radiotherapy [except for colon and rectal cancer] (78).

3.2.2.1. *Colorectal cancer*

There is some evidence to suggest that deprived patients with colorectal cancer are less likely to receive treatment (11, 79, 80). According to a 2010 review examining socio-economic position and inequalities in risk, treatment and outcome for colorectal cancer (11), low SEP colon cancer patients were less likely to receive treatment [surgery, radiotherapy and chemotherapy] but results for rectal cancer were less clear cut. However, within this review the search terms were narrow and a number of relevant papers were not included.

In the above-mentioned review (11) nine studies conducted multivariate analysis and eight included stage. Two only included patients aged 65+ (81, 82). Three (83-85) out of seven studies looking at access to radiotherapy (81, 83-88) found a significant difference by SEP, as did two(82, 85) out of seven studies looking at access to chemotherapy (81-87). Three studies looked at access to surgery (83, 86, 89) but only one (83) showed a significant difference in likelihood of receiving treatment for high compared to low SEP patients. For colon cancer significant differences in receipt of chemotherapy by SEP were found in two (82, 85) out of three papers but, as more mixed results were found for rectal and colorectal cancer and for access to surgery and

radiotherapy, it is difficult to conclude, as the authors did, that treatment differences by SEP can be 'demonstrated consistently'(11). Also, no meta-analysis was conducted. Further studies have also been identified that were not included in the review.

In a large, good quality UK study, deprived patients were less likely to receive treatment within six months of NHS contact [surgery in 95% of cases], adjusted for age and stage (79). However, in a Swedish study the odds of receiving any surgical treatment or any resection were not associated with income or education level [taking into account age, sex, stage, region, hospital type and marital status] (90) and in a UK study deprivation was not associated with lower likelihood of surgery (76) but age, sex, stage and co-morbidities were not taken into account. Another UK study using audit data also found no association between deprivation and receipt of surgery but did find that affluent patients were more likely to undergo curative resection in a univariable analysis (91). Therefore the evidence that receipt of colorectal surgery is affected by SEP is inconclusive and the quality of the studies variable. However, there is some evidence to suggest that the type of surgery received may vary by SEP.

The traditional treatment for colorectal cancer is excisional surgery. For rectal cancer this may require abdomino-perineal excision [APE] which involves the removal of the anal sphincter and leaves the patient with a permanent stoma. The preferred procedure for colonic or high rectal cancer is anterior resection [AR] which allows sphincter retention and appears to improve survival (92).

A review reported that the chances of undergoing APE were higher if the patient was of lower SEP [three UK studies] (11). In a small UK study of 486 patients, those in the most deprived group were less likely to undergo surgery and, if they did, were more likely to have a permanent stoma (93). However, this was a univariable analysis and so other relevant factors were not taken into account. But similar results have been found using better quality multivariable analysis studies.

In a 2010 UK study, patients from deprived areas were less likely to receive anterior resection [AR], the preferred procedure for rectal cancer, taking into account age, sex and year of admission, but not stage (77). A good quality study using NYCRIS cancer registry data also found that a patient was more likely to receive APE if of deprived SEP (92), in a multivariable analysis including stage. In a Swedish study where stage

was included, lower income groups were less likely to receive AR compared to the highest quartile income group. However, when education level was used as the measure of SEP no significant differences were found (90). As education is a less sensitive measure of SEP than income (5), this could help explain the different pattern of results seen.

3.2.2.2 *Lung cancer*

A systematic review of the published evidence for socio-economic inequalities in receipt of lung cancer treatment [surgery, chemotherapy, radiotherapy and any unspecified treatment] has been carried out as part of this PhD. See chapter 7 for the full protocol, methods and results of this review.

3.2.3 *Evidence for inequalities: other factors*

3.2.3.1 *Age*

In a 2001 review (94), it was found that older colorectal patients were less likely to receive adjuvant therapy but, as many of the studies included in the review did not control for stage or co-morbidities, it is difficult to know how much these factors might have impacted on the decision. However, in studies that did take these confounders into account older people did appear to receive less intense adjuvant treatment (94). Other, more recent, studies also confirm that age is significantly associated with receipt of treatment (81-89, 95). Older patients were significantly less likely to receive treatment of any sort.

3.2.3.1.2 *Age: Lung cancer*

Under-treatment of lung cancer in elderly patients has now been recognised as a worldwide issue (70). Older patients tend to be under-represented in clinical trials and so there is less of an evidence base to determine whether treatment would be suitable for them. Elderly patients are often less able to tolerate treatment complications and more likely to experience chemotherapy toxicity but there is no evidence to suggest increased toxicity from radiotherapy, compared to younger patients, and elderly patients who undergo surgery do appear to benefit (70). However, decisions to treat tend to be made using fairly crude measures of suitability such as number of co-morbidities or PS which may result in sub-optimal care for older patients, as the

interaction between age, co-morbidity, patient well-being and suitability for treatment is likely to be complex.

3.2.3.2 *Co-morbidity and performance status*

Higher levels of co-morbidity were significantly associated with a lower likelihood of surgery and adjuvant therapy in some colorectal cancer studies (82, 83, 85, 89), but not all (81).

Although co-morbidity and PS measure different things [number of concurrent health conditions and general health status respectively] both variables may be used as a measure of suitability for lung cancer treatment when patients are assessed. However, it is unclear how well co-morbidity and PS capture this 'fitness for treatment' concept. Where PS is not available co-morbidity score may be being used as a surrogate measure of this. In one of the few studies that looked at both co-morbidity and PS, the authors found that the number of co-morbidities did contribute to PS but were also additionally associated with likelihood of treatment (64).

A recent study found that PS but not the number of co-morbidities, was associated with poorer NSCLC survival (96) suggesting that the presence of co-morbidities is not a particularly good measure of how well a patient was likely to do and so should not be used as a barrier to receipt of treatment if the patient has a good PS score and appears otherwise well.

Another study found that PS did not appear to be a major influence on receipt of treatment according to guidelines, whereas those with a higher number of co-morbidities were less likely to receive guideline treatment for early stage lung cancer (72). Interestingly, they found that co-morbidity was higher in early-stage compared to late-stage patients possibly because lung cancer was picked up earlier in patients who were regularly monitored for other conditions. However, patient age rather than PS or comorbidity appeared to be the main factor on which choice of treatment was based (72).

3.2.3.3 *Sex*

Sex has been less consistently associated with access to treatment. In some colorectal cancer studies men were found to be more likely to undergo surgery resulting in

sphincter loss [APE], probably due to differences in pelvic anatomy between the sexes (94). A study using NYCRIS cancer registry data also found that a patient was more likely to receive APE if male (92). Women were more likely to receive AR compared to men (77, 90). Sex was also found to be a significant factor in the likelihood of any surgery in other studies (83, 86, 89, 90). Sex was not a significant factor in access to chemotherapy or radiotherapy in the majority of studies examined (81, 83, 86-88) but was in two (84, 85) and in a further study that looked at chemotherapy alone (82).

3.2.3.4 *Ethnicity*

In the USA differences in access to colorectal cancer treatment and outcome have been observed by race (94, 97) but some of these differences may also be related to differences in income and SEP (85, 97). There are also issues when comparing American and UK studies due to the differences in the healthcare systems, as within non-universal health care systems the type of insurance held can affect access to treatment (85).

3.2.3.5 *System factors*

The introduction of a multidisciplinary team [MDT] to a hospital in Glasgow resulted in an increase in the number of non-operable NSCLC patients receiving chemotherapy and was also associated with an increased rate of staging, compared to an earlier cohort who were assessed only by a medical oncologist (98).

A 2001 review of patient and provider characteristics on treatment and outcomes in colorectal cancer found that patients were more likely to receive sphincter-saving surgery [i.e. AR] when they were treated by a surgeon with a high volume caseload or who had undergone subspecialty training (94). Removal of sphincter [i.e. APE] was more likely if operated on by a surgeon undertaking fewer than seven cases per year (92).

3.3 Summary: Socio-economic inequalities in receipt of treatment

From this narrative review of socio-economic inequalities in receipt of treatment for a number of cancers, it can be seen that there is some evidence that receipt of treatment is socio-economically patterned. However, this is not clear cut and many studies do not take into account cancer stage at diagnosis, number of co-morbidities or

the general health status of the patient, all factors that might potentially vary by SEP and thus help explain socio-economic inequalities in treatment. No systematic review of the evidence taking into account study quality [including control for appropriate confounders] has been conducted and this is required in order to clarify whether inequalities in receipt of treatment are found for lung cancer.

The next chapter will examine the evidence for socio-economic inequalities in time to presentation, referral, diagnosis, and treatment for cancer, as well as the potential reasons for this.

Chapter 4. Intervention-generated inequalities in cancer care: time intervals

4.1 Background

In this chapter, the background relating to the importance of early diagnosis and measures to improve this will be described. The evidence for socio-economic inequalities in time to presentation, referral, diagnosis and treatment, and the reasons for this, will then be examined.

4.1.1 *Delay or interval?*

In the earlier literature the term 'delay' appears frequently. However, latterly this mostly appears to have been replaced with the term 'interval' and the discussion centres more around early diagnosis rather than a delay in diagnosis. The use of 'delay' implies that the time taken is longer than is desirable or acceptable but, within studies that use this term, it is not always the case. It may be appropriate to use 'delay' when a time interval is longer than a specified target time but otherwise the term 'interval' will be used. However as previous studies have used 'delay' the term will still appear in this chapter, when referencing these studies.

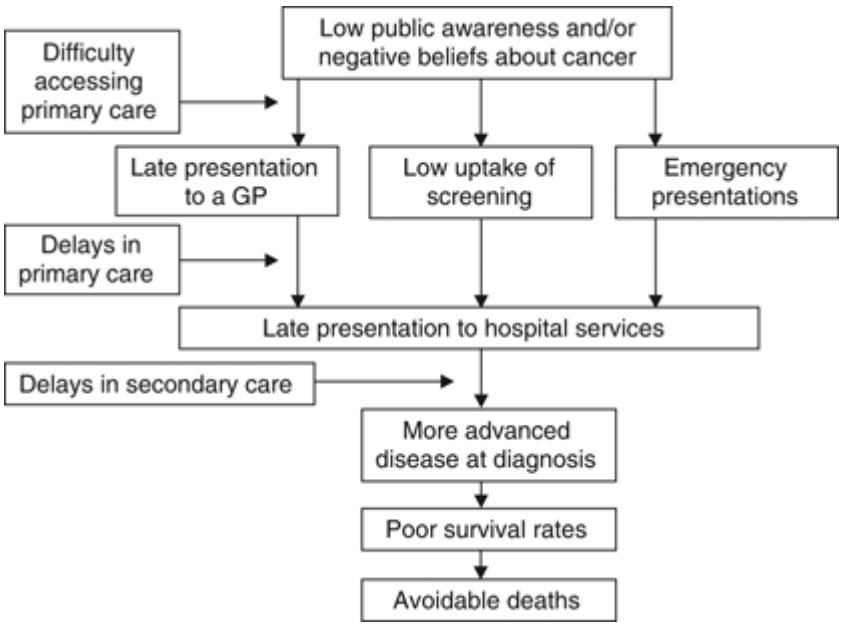
4.1.2 *Early diagnosis*

Early diagnosis of cancer is thought to be important for improving outcomes, as survival is better for those diagnosed with early-stage cancer (99). Early diagnosis may also result in longer intermediate survival for patients with SCLC and later stage NSCLC. Early palliative treatment can greatly relieve distressing lung cancer symptoms such as pain, breathlessness and persistent cough [Dr M Peake, *personal communication*]. Patient anxiety can also be greatly ameliorated by prompt referral and diagnosis.

In England the National Awareness and Early Diagnosis Initiative [NAEDI] is a scheme designed to encourage early presentation of patients to primary care and to improve GP cancer recognition and referral. It proposes that delays may lead to diagnosis at a later disease stage and thus result in 'potentially-avoidable' deaths (99). It has also been suggested that inequalities in delay might contribute to socio-economic differences in cancer survival (99).

A NAEDI delay pathway has been constructed to suggest why delay at different points on the pathway may occur and how these might impact on survival [fig 4.1]. This model dovetails in many respects with the proposed model for intervention-generated inequalities (7), as it considers access to primary care, as well as uptake of, and delay in, care; all of which may result in inequalities in outcome. However, the model does not break down into detail the stages in primary and secondary care where delays might occur.

Figure 4.1. The NAEDI pathway [99]



4.1.3 *Definition of important time points and target times*

In the research to date, poorly defined definitions of the important time points that characterise delay periods have resulted in a number of inconsistent and incomparable studies. To address this issue, an international consensus working group [CWG] has now formulated a standard set of definitions relating to delay intervals and time points and a checklist for researchers examining early diagnosis (100). Therefore these will be utilised for this present study.

In the UK the National Cancer Plan [2000] proposed target time intervals of 14 days from urgent GP referral to first outpatient assessment, one month [31 days] from diagnosis [decision to treat] to treatment, and two months [62 days] from GP referral to first treatment, to be in place by 2005 (24). A 2007 study of 342 patients seen in a

Manchester hospital between 2003 and 2005 found that although all patients were seen within the 14 day referral interval, the 62 day treatment target was not being met (101). This was attributed to complex patient pathways and delays in investigations and initiation of treatment.

4.1.4 Theoretical models of delay

The CWG suggested that there is lack of an underlying theoretical model to explain delay (100). However, two delay models have been used in the literature: the Hansen and Anderson models. An early model of cancer delay, the Anderson model, attributed the majority of delay to patient rather than system factors. However, it has been suggested that this may be 'an artefact of research focus' and that system delay may be an equally important but under-researched area (102). For example, figure 4.2 shows the detailed diagnostic and staging clinical pathway for lung cancer [NICE guidance 2011] (22). Patients with suspected lung cancer are often initially referred for a chest x-ray and the diagnosis confirmed by bronchoscopy. Other investigations including CT scans may then be deployed to help determine the most appropriate treatment (24). Hence there are a number of system stages where delays can be introduced.

A recent review looked at the application of the Anderson Model of delay in cancer diagnosis, as the authors proposed that the use of a robust theoretical framework could improve the investigation of delay, and help develop interventions to reduce time to presentation, diagnosis and treatment (103). They produced a refined Anderson model that took into account system and disease factors, as well as patient factors, and split time intervals into appraisal, help-seeking, diagnostic, and pre-treatment intervals [Fig 4.3]. This results in a model that is fairly similar to the Hansen model which also considers patient, doctor and system delay, with further sub-divisions [Fig 4.4] (104). These models, when used in conjunction with NICE treatment decision matrices [Fig 1.1 shows the matrix for lung cancer] (22), can allow examination of intervention-generated inequalities at all stages of the cancer care pathway.

Figure 4.2. Diagnostic and staging clinical pathway for lung cancer [22]

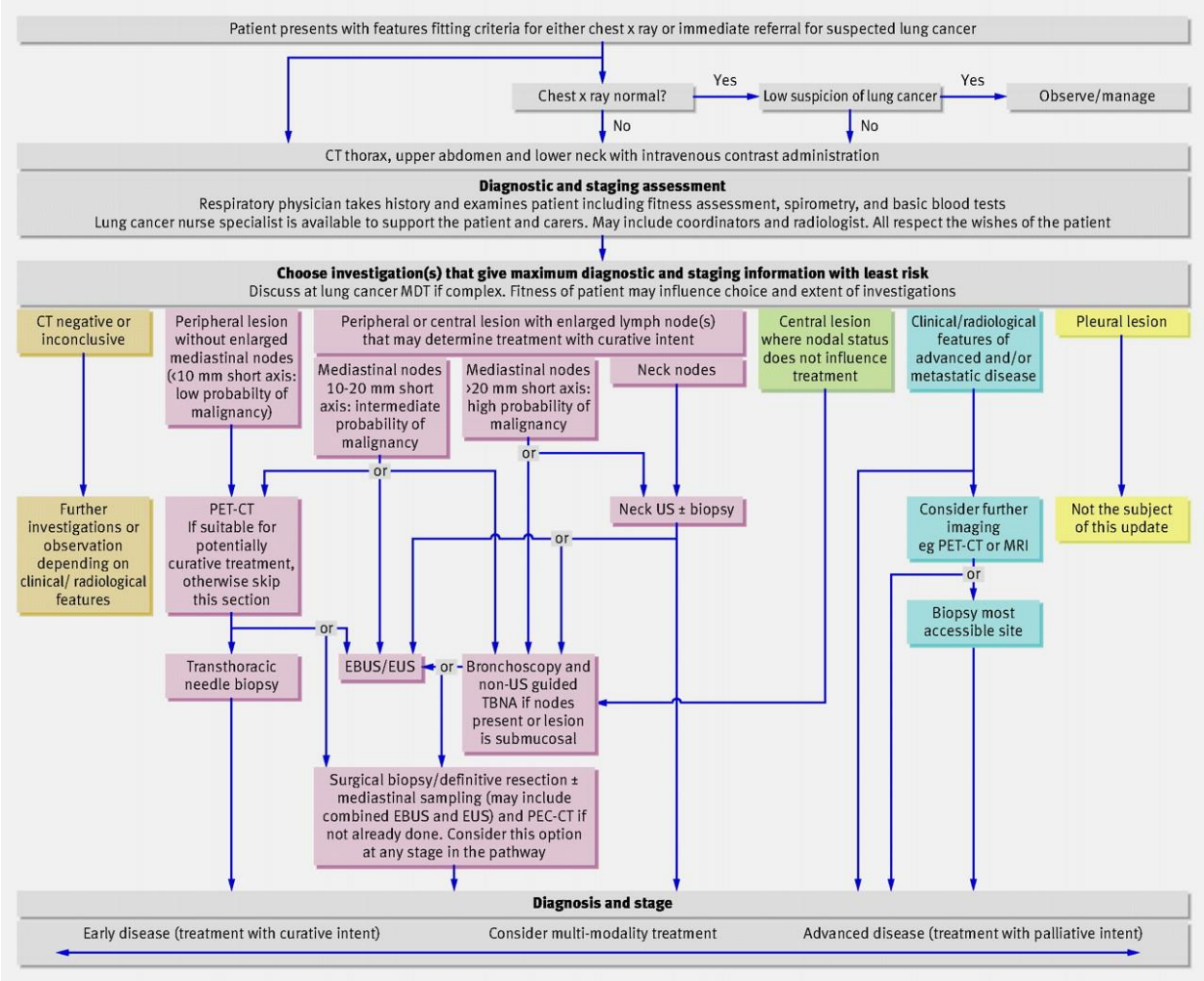


Figure 4.3. Updated Anderson model of delay [103]

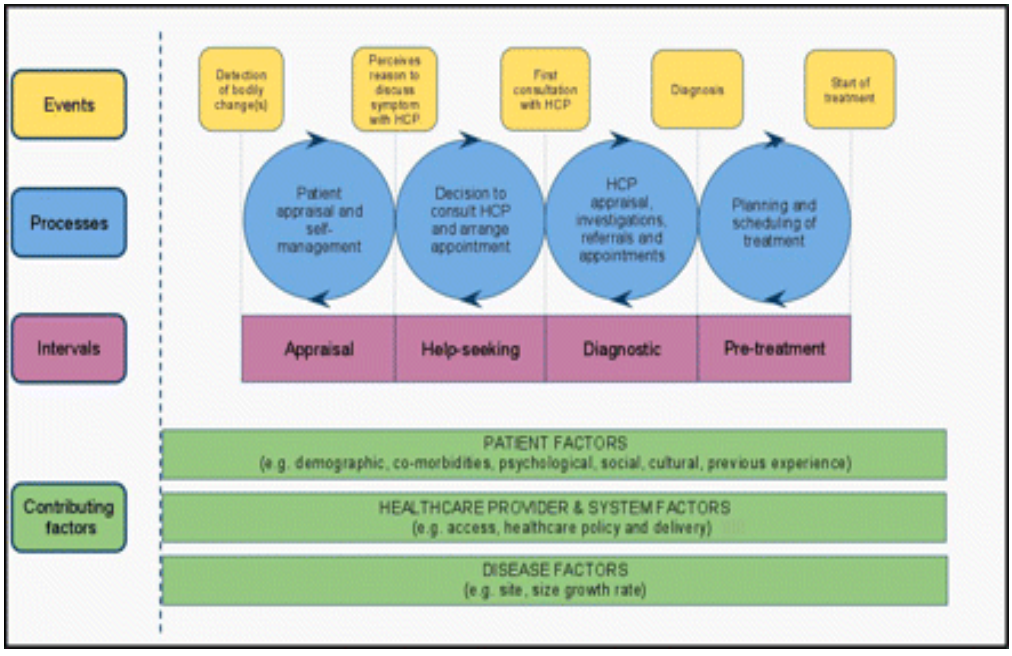
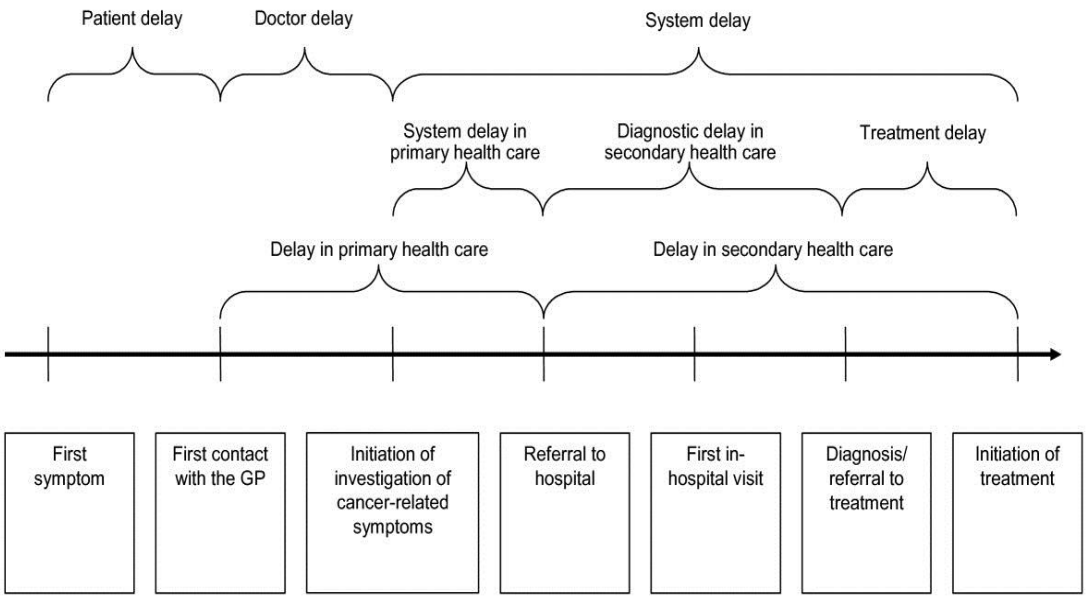


Figure 4.4. Hansen model of delay [104]



I will now consider the intervals on the care pathway where delay might occur and the potential reasons for this. I will also examine some of the previous problems in measuring delay and the different ways that this has been done, with the resultant difficulties in comparing studies. Evidence for socio-economic differences in time to presentation, referral, diagnosis and treatment within the cancer care pathway, taking into account patient and system factors that may influence delay, will also be examined, including the evidence specifically relating to lung cancer.

4.2 Evidence for inequalities in cancer care time intervals

Table 4.1 summarises the previous evidence from studies examining inequalities in lung cancer care time intervals, by SEP. The table details the time interval examined, the country of the study, years of diagnosis, size of the study, and the median time for the interval in the lowest and highest SEP group [if reported], as well as the type of analysis carried out [whether univariable or adjusted for confounders in a multivariable analysis]. The evidence from the lung cancer studies included in this table, as well as the evidence for other cancers, is discussed in more detail below.

Table 4.1. Summary of previous evidence from studies examining lung cancer time intervals and SEP

Interval								low SEP associated with:		
Specific Interval/ *proxy measure*	study	Country	N	Years of Diagnosis	Median/ *mean* delay	Method	Further Info	Longer delay	Shorter delay	No assoc
Patient										
Stage at presentation	Lyratzopoulos et al (2012) [68]	England	13,286	2006-2009	Not calculated	OR of advanced stage at diagnosis				X
Stage at presentation	Lyratzopoulos et al (2012) [66]	England	16,714	2006-2010	Not calculated	OR of advanced stage at diagnosis				X
Patient	Macleod et al (2009) [105] review	USA	34, 23, 119	Pre 1973, 1975 + 1990	Not shown	Not detailed		X (1/3)		X (2/3)
Primary care										
First consultation to referral	Macleod et al (2009) [105] review	Norway	40	pre1996	Not shown	Not detailed		X		
Referral										
Contact with GP – hospital appointment	Neal and Allgar (2005) [106]	England	2950	2002 patient survey	*30* (professional) *30* (unskilled)	Generalised linear modelling				X
Diagnostic										
FHA to diagnosis (secondary care delay)	Neal and Allgar (2005) [106]	England	3199	2002 patient survey	*17 (*professional) *13 (*unskilled)	Generalised linear modelling				X
Referral to diagnosis	Berglund et al (2010) [73]	Sweden	3370	1996-2004	17 (high education) 32 (low education)	Kaplan Meier. Time to diagnosis by education level		X		
Image-diagnosis	Yorio et al (2009) [107]	USA	482	2000-2005	16 (6-43)	Cox regression				X
Referral - diagnosis	Dalton et al (2011) [108]	Denmark	18,103	2001-2008	Not calculated	Logistic regression: OR of diagnostic delay > 28 days	16,713 with stage and diag date	X		
Treatment										
Referral-treatment	Campbell et al (2002) [86]	Scotland	661	1995-1996	33 (15-104) high SEP 25 (13-77) low SEP	Kaplan Meier, Cox regression				X
Image-treatment	Yorio et al (2009) [107]	USA	397	2000-2005	50 (30-84) high income 65 (39-110) low income	Cox regression	Sig at uni but not multivariable level			X
Diagnosis-treatment	Yorio et al (2009) [107]	USA	299	2000-2005	29 (17-55) high income 36 (21-56) low income	Cox regression	Sig at uni but not multivariable level			X
Detection- surgery	Saint-Jacques et al (2008) [109]	Canada	108	2005	107 (73-141) results by education level not shown	Multifactorial regression	Those who received surgery inc (108 out of 540 NSCLC)			X

4.2.1. *Patient interval*

4.2.1.1 *Definition and background*

Patient delay can be defined as the time between onset of symptoms and initial presentation to the GP or other healthcare professional (110). It has recently been recommended that the term 'patient delay' should no longer be used, and that 'patient interval', split into an 'appraisal interval' and help-seeking interval', is more meaningful and so should be adopted (100). However as I am reviewing previous literature where only the term 'patient delay' has been utilised, it seems appropriate to still include this term here.

It is difficult to measure patient delay as this requires the patient to accurately remember when they first noticed the onset of symptoms, which may be subject to recall bias. Unlike system delay, which can be examined using secondary data, the calculation of patient delay generally requires patients to be interviewed or to complete a questionnaire post-diagnosis. Alternatively, stage at diagnosis can be used as a proxy measure of late presentation.

4.2.1.2 *Evidence for inequalities in patient interval*

Time to consultation might be influenced by fear or by poor symptom recognition and disease awareness, and this awareness may be lower in more deprived socio-economic groups (111). In a systematic review summarising risk factors for delayed presentation for a number of common cancers an association was found between lower SEP and increased delay for upper GI and urological cancer, older age and patient delay for breast cancer and lower education level and delay for breast and colorectal cancer (105). Generally, not recognising the seriousness of symptoms was found to be a significant factor in increasing delay in presenting, especially when symptoms were vague and non-specific (105).

The availability of social support positively influenced time to presentation for breast, colorectal and endometrial cancer but did not appear to reduce delay for lung, upper GI or urological cancer (105). Older age but not SEP was associated with shorter patient delay in a Dutch study including 10 cancer types (104).

Systematic review evidence identified co-morbidity, pain and social support as potentially important factors in reducing patient delay in presenting with suspected colorectal cancer but age and sex were not found to have an influence (112). The evidence for SEP was more mixed. A number of older studies found no relationship between lower SEP and increased delay. Other studies found that lower levels of education and residing in a rural location increased delay (112). Patient delay was found to be longer for rectal than for colon cancer (112, 113) possibly because the symptoms associated with rectal cancer such as rectal bleeding are often found in more benign conditions but embarrassment may also be a factor (112). An Italian study found that patients with lower levels of education had non-significantly longer time intervals between colorectal cancer symptom onset and first consultation (114).

4.2.1.2.1 *Evidence for inequalities in patient interval: Lung cancer*

A 2009 review of two systematic reviews looking at risk factors for delay in common cancers found only three small, old studies that considered SEP and patient delay for lung cancer and only one of three found an association (105). Stage at diagnosis can also be used as a proxy measure of late presentation. Although socio-economic inequalities in stage at diagnosis have been noted for some cancers which might suggest that there are differences in timeliness of patient presentation by SEP (66), three studies examining socio-economic inequalities in stage at diagnosis for lung cancer did not find any significant differences by SEP (66, 68, 115).

The availability of social support did not appear to reduce delayed presentation for lung cancer (105). A small qualitative study of patient delay in lung cancer did however find that family support decreased delay in reporting symptoms. Many patients delayed going to the GP as they thought that they would be blamed for their illness due to their smoking or, if they were not a smoker, they thought that lung cancer was highly unlikely (116). Guilt and fear may also be factors that influence delay (102). In a Scottish study, more deprived rural-dwelling lung cancer patients did not take longer to consult than affluent urbanites. However, living alone and having a long smoking history increased delay (117). A small Turkish study that interviewed 48 lung cancer patients who delayed presenting found that the most common reason for patient

delay was due to ignoring symptoms but that socio-cultural and economic factors were also important (118).

4.2.2 *Primary care interval*

4.2.2.1 *Definition and background*

Within the primary care setting, the time from first presentation to the GP until the referral date can be defined as primary care interval or referral interval. Delays could occur in initiating primary-care investigations and ordering tests before ultimately referring the patient for secondary-care investigation.

NICE Cancer referral guidelines were introduced in 2005 and are designed to assist GPs to identify patients at risk of cancer (119). However, although lung and colorectal cancer are common an average GP is likely to see only one or two new patients each year (23, 120) and many patients present with vague symptoms. If symptoms are not immediately suggestive of cancer a 'treat, watch and wait' period is a suggested management option for colorectal cancer (119), which can increase delay. If colorectal cancer is suspected then abdominal and rectal examinations and a full blood count should be carried out. Patients presenting with co-morbidities can also make diagnosis more difficult (102).

4.2.2.2 *Evidence for inequalities in primary care interval*

Higher SEP patients [measured by income or education] had shorter delay from first contact with the GP to initiation of primary care investigation [doctor delay] than less privileged patients, in a Danish cancer study including but not separating out lung cancer (104). The authors suggest that wealthier and better educated patients are better able to describe symptoms and thus speed up the investigation process or that doctors relate better to these patients and that, possibly unintentionally, these patients are given a speedier investigation (104). However patient numbers were small and inconsistencies were found between men and women.

It has been suggested that socio-economic differences in communicating and presenting cancer symptoms to health professionals may result in longer delays for those who are less 'convincing' (111). Some evidence of delay was seen for those

(mainly women) who consulted frequently and were subsequently diagnosed with colorectal cancer, although SEP was not examined (112).

A small Italian study of 137 colorectal cancer patients found that patients with lower levels of education had longer time intervals from first consultation to surgical referral but that this delay was not significant (114). A 2008 review of influences on pre-hospital delay of colorectal cancer found that 'initial misdiagnosis, inadequate examination and inaccurate investigation increased practitioner delay' (112). Older patients were referred more quickly and there was some evidence of lower SEP patients experiencing longer delay but no relationship was shown between sex and primary care delay (112). Appropriate use of guidelines may also reduce colorectal cancer delay although the evidence was limited (112).

4.2.2.2.1 *Evidence for inequalities in primary care interval: Lung cancer*

No individual lung cancer studies were identified that examined inequalities by SEP over the primary care interval. One study identified in a systematic review (105), that looked at a number of cancers and included only 40 lung cancer patients, suggested that higher education reduced delay. However, lower SEP was not associated with pre-hospital delay for any of the six cancers [breast, colorectal, lung, ovarian, prostate, non-Hodgkin's lymphoma] looked at in a UK study of over 65,000 patients (106) although within this it was not possible to separate-out patient and primary care delay.

4.2.3 *Primary care to secondary care referral interval*

4.2.3.1 *Definition and problems*

The date of referral is considered to be the time point where there is a transfer of responsibility from primary to secondary care (100). Delay from GP referral date to secondary care investigation [generally first outpatient assessment or first hospital appointment] can be categorised as primary care to secondary care referral delay or as investigation delay. However, within the literature this is mostly just referred to as referral delay (121, 122). However, referral delay can also be measured from first contact with the GP until first hospital appointment (123), so can include both primary care referral delay, which is delay prior to the referral date, as well as post-referral delay (11).

Patients in England and Wales with suspected cancer should be seen by a specialist within two weeks of GP referral (24) but it appears that delays are still experienced in waiting for tests and in the use of non-urgent referrals, as well as other delays caused by administrative and communication problems.

4.2.3.2 *Evidence for inequalities in referral interval*

Younger age was associated with increased referral delay for lung, breast, colorectal and prostate cancer and women experienced longer delays compared to men for colorectal cancer but lower SEP was not associated with referral delay [here defined as time from first contact with GP to first hospital appointment] for any of the six cancers looked at in a UK study (106). However, mean rather than median time was used here and as delay intervals tend to be non-normally distributed [right skewed] then the use of mean can artificially inflate the delay values seen and so is not necessarily a very useful measure. This can be seen in a lung cancer study that reports mean and median delay values, where mean delay is much larger than median (121).

Referral delay was examined in an MPhil thesis looking at pancreatic cancer (29) which found that time from GP referral to hospital investigation was significantly shorter for less deprived patients in a multivariable analysis including age, sex and co-morbidity.

In another study, age, sex, ethnicity and marital status did not appear to influence the likelihood of urgent referral for lung, colorectal, prostate or ovarian cancer (124). SEP was not examined.

4.2.3.2.1 *Evidence for inequalities in referral interval*: *Lung cancer*

In a small UK study of 247 lung cancer patients, 54% of these were referred from their GP and the other 46% were non-GP referrals such as those presenting via casualty. Urgent patient referral intervals were short, with a median of 1 day [IQR 1-5]. However no time period was reported for non-urgent referrals (125). Median referral delay was 8 days in a Finnish study (121).

Although SEP was not examined, age, sex, ethnicity and marital status did not appear to influence the likelihood of urgent referral for lung cancer (124). Younger age was associated with increased referral delay [here defined as time from first contact with GP to first hospital appointment] for lung cancer but lower SEP was not associated

with referral delay, in a large UK study (106). However, mean rather than median time was used.

4.2.4 *Secondary care interval*

The secondary care interval can be further broken down into diagnostic and treatment intervals although both of these measures can also include elements of patient and primary care delay, depending on how they have been measured.

4.2.4.1 *Diagnostic interval – definition and problems*

Diagnostic delay is defined as the delay in receiving a diagnosis but there is confusion in the literature over the time period measured. It can be measured from onset of symptoms (113, 126), referral date (113) and from secondary-care investigation (127) to diagnosis. Diagnostic delay may contain elements of both patient delay and healthcare delay (113) and it has been suggested that patient and primary care delays account for over two-thirds of reported diagnostic delay (128). However, a Cuban study [96 patients] estimated that patient delay accounted for 18 days of delay and the health-care system for 62 days (126) [but again mean rather than median time was used]. The lack of consistency in defining diagnostic delay makes comparison between studies difficult.

The type of referral route might be important in determining diagnostic delay. In a UK study using national cancer survey data, patients who were referred via their GP had longer diagnostic delay than those who were not (123).

Date of diagnosis can be defined in a number of different ways and it is not always clear within studies how date of diagnosis has been derived. The European Network of Cancer Registries uses a priority hierarchy to define date of diagnosis, with 6 categories; starting off with the date of histological or cytological confirmation of malignancy [which can be derived from 3 different hierarchical time points]; then date of hospital admission; down to, with lowest priority; date of death if cancer is only identified at autopsy (100). Therefore, it is possible that within each study patients have a date of diagnosis derived at a number of different time points. In order to calculate meaningful diagnostic and treatment intervals it is necessary to exclude those who have a diagnosis only after death but, even after excluding these records, a

high level of inconsistency in diagnosis date may remain. If differences in diagnostic date occur in a random manner then this increases error. However, if there are systematic differences in the way that date is recorded according to SEP [although I could find no evidence for this] then this may lead to bias and have a serious impact on our ability to accurately measure interval inequalities.

4.2.4.2 *Evidence for inequalities in diagnostic interval*

In a UK study lower SEP was associated with increased total diagnostic delay for prostate but not colorectal or breast cancer (106), but again this included an element of patient delay. In the same study SEP was associated with secondary care diagnostic delay for colorectal, ovarian, prostate and breast cancer (106). However, no inequalities in time from first hospital appointment to diagnosis in high compared to low SEP groups were found in a pancreatic cancer study in a model including age, sex and co-morbidity but not stage (29).

In a Scottish study diagnostic delay for colorectal cancer was shown to be longer for those living in a rural location further from a cancer centre (86).

4.2.4.2.1 *Evidence for inequalities in diagnostic interval: Lung cancer*

Socio-economic position was not associated with secondary care delay [from first hospital appointment to diagnosis date] for lung cancer in a UK study of over 3,000 patients (106). Nor was it associated with increased total diagnostic delay for lung cancer (106), but this calculated the time from first symptom to diagnosis, so included an element of patient delay. Mean rather than median delay was also used. A small US study looking at time from imaging to diagnosis also found no association with SEP when using either education or income as the measure (107).

In contrast, a Swedish study did find that lower SEP lung cancer patients experienced longer delays between referral and diagnosis, with a median wait of 32 days for low education and 17 days for high education level patients (73). However, this was a univariable analysis. But a large, good quality Danish study of over 18,000 lung cancer patients also found that those with a higher education level were more likely to have a diagnosis within 28 days from referral [the target waiting time] compared to those with shorter education, adjusted for age, sex cohabitation status and co-morbidity, in

both early and late stage patients (108). A significant association was only found for early stage patients when income was used as the measure of SEP however.

4.2.4.3 *Treatment interval – definition and problems*

The treatment interval is generally defined as the time between diagnosis and treatment (113, 129). However, it can also be measured as time from first symptoms (130), time from first consultation (79) or receipt of referral letter (122) to treatment, again making comparison between studies difficult.

There may be valid reasons why adjuvant therapy is delayed after curative surgery. These could include post-operative complications, longer recovery due to cancer complications, and poor pre-operative performance status due to presence of co-morbidities, advanced stage and age (131). Post-operative complications may also reduce the likelihood of chemotherapy after surgery.

4.2.4.4 *Evidence for inequalities in treatment interval*

SEP [measured by household income] did not affect time from diagnosis to treatment for cancer in a Canadian study. Older patients and women had lower waiting times (129). Women with high household income experienced shorter system delays [from initial primary care investigation to treatment] than those less economically privileged, in a Danish cancer study (104).

In a large, good quality study using data from over 71,000 patients from 3 UK cancer registries and employing an area-based measure of SEP, deprived colorectal cancer patients were more likely to receive late treatment (79) [in a model including SEP, stage, age and time to treatment from first contact]. In a German study of 86 patients treatment delay for colorectal cancer [measured as total time from first symptoms to treatment] was associated with SEP [as was type of cancer and marital status but not age or sex] (130). However, this measurement of treatment delay included patient as well as practitioner delay and the patient delay actually accounted for over 70% of the overall delay. A French study found no influence of occupation [as a measure of SEP] on time to treatment for colorectal cancer (132).

4.2.4.4.1 *Lung cancer*

4.2.4.4.1.1 *Length of time to treatment interval*

A number of lung cancer studies report time to treatment intervals. One small UK study found that the time from GP referral to treatment was a median of 60 days (IQR 44-85) with the time from secondary care specialist referral to treatment varying by treatment type [25 days for surgery, 16.5 days for chemotherapy and 43 days for radiotherapy] (101). A small Indian study of 165 patients found that median time from diagnosis to treatment was 20 days (133) and, when they looked at a number of older studies, these found times varied from 10 to 30 days [but, as they reported, these used mean rather than median time so need to be interpreted with caution]. A small UK study from 1998 found that median time from receipt of referral letter to treatment was 48 days (122). A Finnish study reported lung cancer treatment delay as median 15 days from diagnosis and 30 days from first visit to specialist (121).

4.2.4.4.1.2 *Evidence for inequalities in treatment interval*

In a Swedish study older patients had longer delay in an unadjusted analysis of time to treatment for non-small cell lung cancer. SEP was not measured (134). A small Scottish study of time between referral and first treatment for lung cancer found no association between SEP and time to treatment (86) in both univariable and multivariable analyses [taking into account age, stage and health board]. A small American study found a univariable association between income [as a measure of SEP] and time from image to treatment, but not when education was used. In the multivariable analysis only type of hospital remained significantly associated, with those treated in a public hospital having significantly longer delay [median 76 days] than those treated privately [45 days] (107). A small Canadian study found no association between education level and time from detection to surgery (109).

4.3 Summary: Socio-economic inequalities in time intervals

The evidence for the influence of SEP on time to consultation, referral, diagnosis, and cancer treatment is inconclusive and further investigation is required.

A review of the current evidence for lung cancer, as discussed in this chapter, is shown in table 4.1. Results are contradictory for time to diagnosis [two studies found

inequalities in time from referral to diagnosis and two found no association in time from FHA to diagnosis and image to diagnosis, with SEP]. No association was found between SEP and time to presentation [using stage at diagnosis as a proxy] and time to treatment. However, very few studies used median time, most studies were very small and had low statistical power [particularly in the time to treatment analyses] and many employed only univariable analysis and so were of poor quality. Inconsistent measures of time period were also used making comparison between studies difficult. Therefore the evidence for socio-economic inequalities in delay for lung cancer is inconclusive.

The evidence for whether delay contributes to socio-economic differentials in survival is considered in section 5.4 of chapter 5, which examines inequalities in survival.

Chapter 5. Inequalities in cancer survival

This chapter examines the evidence for inequalities in cancer survival, why inequalities might be found and what factors might influence inequalities in survival.

5.1 Introduction

Socio-economic inequalities in survival have been described for most common cancers (135) and although introduction of the NHS Cancer Plan in 2000 may have improved overall cancer survival there does not appear to be a concurrent reduction in the deprivation survival gap in England (136). Three recent studies have looked at relative survival for common cancers in England, Wales and Scotland. They all found that although cancer survival was improving the deprivation gradient was getting steeper (25, 136, 137).

Cancer survival may be influenced by patient-related factors such as performance status and co-morbidities (138), tumour factors relating to stage and aggressiveness of the cancer, and to service-related factors such as treatment decisions by the multi-disciplinary team [MDT] (102). Post-operative complications may also be relevant, as might delay.

5.2 SEP and cancer survival

5.2.1 *Why might socio-economic inequalities in cancer survival be found?*

Variation in co-morbidity, stage at diagnosis and in receipt of treatment have all been suggested as potential explanations for socio-economic inequalities in cancer survival, although few studies have adjusted for these factors or looked at how they vary by SEP (137). Poorer survival is generally attributed to later presentation by lower SEP patients. A 2006 review summarised a decade of research on the association between SEP and cancer survival (26) and although stage at diagnosis did seem important in determining likelihood of survival [particularly for colorectal and breast cancer] the authors felt that socio-economic differences in 'access to optimal treatment' (26) partially explained survival differences.

One recent study has attempted to examine receipt of treatment and survival by SEP for breast and colorectal cancer, using the theoretical framework of the 'inverse equity

law' to determine whether survival inequalities widen after the introduction of a new treatment, on the assumption that it is more likely to be offered to the more affluent patients (35). However, as they were not able to determine the actual treatment received by patients but were only able to graph the date of introduction of a new treatment and the survival trends after that time, it was difficult to draw any clear conclusions.

It has been suggested that social support and being married may lead to better cancer survival (26, 139). The less affluent tend to have lower levels of support although the effects may differ between the sexes (139). Differences in smoking rates may be important. A Norwegian study of women found that smoking status prior to diagnosis was a predictive factor for socio-economic variation in cancer survival (140).

5.2.2 *Evidence for socio-economic inequalities in cancer survival*

Stage at diagnosis appears to be the main prognostic factor for colorectal cancer survival (141) but survival rates have consistently been shown to be worse for those with lower SEP (10, 11, 79, 142-144). A number of studies have also shown that survival rates are lower for breast cancer patients who reside in more deprived areas (137, 143, 145-148). There is evidence for a socio-economic gradient in survival for lung cancer in some studies, with poorer survival in more deprived groups (73, 149-151), but not in others (143, 152, 153), although no studies found an inverse gradient – see table 5.1.The evidence will be explored in more detail below.

5.2.2.1 *Colorectal cancer*

In a UK study looking at five year colorectal cancer survival, area-based socio-economic deprivation was associated with increased mortality (142). Age, stage and number of co-morbidities were also significant. Similar results were found in a Danish study (144) where it was suggested that co-morbidity may partly explain the social gradient in survival. However, in another study it was shown that survival was less likely if co-morbidities were present but a socio-economic gradient was not found (138).

Deprived colorectal cancer patients had poorer three-year survival compared to the more affluent using data from three UK cancer registries, in a large, good quality study (79). However, no differences in survival were seen for those patients who had

treatment within one month of diagnosis but the socio-economic survival gradient remained in those who had later or no treatment, even when age and stage were taken into account (79). Earlier access to treatment attenuated socio-economic differences in survival in this cohort suggesting that improved access to treatment for all might lead to an overall improvement in outcome (79). Another study appears to support this finding, as within a randomised controlled clinical trial of chemotherapy and radiotherapy for colorectal cancer, when crude and relative survival at one and five years were analysed by socio-economic deprivation then the excess hazard of death was not significantly higher in the more deprived groups, adjusted for age, sex, stage and cancer site (154), suggesting that equal treatment results in equal outcome, regardless of SEP (154). However, it may also be that the type of patient who is considered for a clinical trial [generally younger and fitter] may also have an influence here.

A recent study concluded that excess deaths occurred in the first month post-diagnosis in more deprived colon cancer patients but this excess persisted for longer in deprived rectal cancer patients (155) although stage and co-morbidity were not included in the analysis. Lower SEP was associated with a higher risk of 30-day post-operative mortality (65) although much of this effect was explained by differences in grade and stage of the tumour and by emergency compared to elective surgery. In this study more deprived patients presented with later stage cancer (65) in contrast to another study which did not find this (156). This small but good quality study (156) found better survival for more affluent patients who underwent curative surgery. However, there were no socio-economic differences in stage, mode of presentation or treatment offered and so they suggested that outcome differences might be related to a more compromised tumour-host response in the more deprived patients.

5.2.2.2 *Lung cancer*

Table 5.1 summarises the results from studies located in a review of the literature that examined the socio-economic gradient in survival for lung cancer. Details of the country of study, study size, years of diagnosis, and confounders included are shown, as well as the hazard ratio of survival in the lowest compared to the highest SEP group

for univariable and where conducted, multivariable analysis. Some contradictory findings can be seen.

A recent UK study found that three-year survival in 1828 early-stage NSCLC patients was 50% in the most affluent group and 39% in the most deprived (157) with a univariable HR=1.35 [95% CI 1.07 to 1.70]. However this HR was attenuated and became non-significant [HR=1.24 (95% CI 0.98 to 1.56)] in a multivariable model including age, sex, co-morbidity and receipt of surgery. A similar result was seen in an earlier, smaller UK study that examined one-year survival. A significantly decreased univariable OR of survival was found in the lowest compared to the highest SEP group and this remained when age, sex, histology, basis of diagnosis, number of symptoms, consultant specialty and stage were included in the model but not when receipt of treatment was included (158). The authors suggest that poorer survival in more deprived patients may therefore be due to differences in receipt of treatment rather than case mix variation (158). In a clinical trial education-level was not associated with survival when standard treatment was received by all (159) which would support this theory. However, two studies using lung cancer audit data did not find socio-economic inequalities in survival whether or not treatment was included (152, 153).

Table 5.1. Summary of previous evidence from studies examining likelihood of survival by SEP (in most deprived [low SEP] compared to least deprived [high SEP] group), for lung cancer

						Univariable HR	Multivariable HR	Low SEP associated with:		
Study	**Country**	**N**	**Years of Diagnosis**	**Confounders**	**Further information**	**HR (IMD=5)**	**HR (IMD=5)**	**Higher HR**	**Lower HR**	**No association**
Berglund et al (2012) [157]	England	1,828	2006-2008	Age, sex, co-morbidity, receipt of surgery	3 year survival – early stage	1.35 (1.07 to 1.70)	1.24 (0.98 to 1.56)	X		X
Cheyne et al (2013) [115]	England	1,432	2008-2010		Univariable Kaplan-Meier only 1 year survival	39% in high SEP 33% in low SEP				X
Jack et al (2006) [158]	England	695	1998	Age, sex, histology, basis of diagnosis, stage, number of symptoms, consultant specialty, treatment	OR of survival NOT HR of death 1-year survival	0.63 (0.35 to 1.13) P for trend = 0.02	0.84 (0.24 to 2.45) P for trend = 0.19	X		X
Jones et al (2008) [160]	England	34,923	1994-2002	Age, sex, stage, histology, treated at cancer centre, travel time	Cont measure NYCRIS data	--	1.001 (1.000 to 1.002)	X		
Riaz et al (2012) [161]	England	77,349	2004-2006	Age, sex	HR inc with age and derivation in full dataset but not by deprivation in receipt of surgery dataset	Data not shown	Data not shown	X		X
Rich et al (2011) [153]	England	48,453	2004-2007	Age, sex, PS, histology, stage		1.03 (0.97 to 1.09)	1.00 (0.95 to 1.06)			X
Rich et al (2011) [152]	England	34,365	2004-2008	Age, sex, stage, PS, ethnicity, CCM, surgery, surgery centre, radio centre, trial centre	Clustering by NHS trust	1.04 (1.00 to 1.08)	0.99 (0.94 to 1.05)			X
Berglund et al (2010) [73]	Sweden	3,369 (1,405 women)	1996-2004	Age, sex, histopathology, PS, smoking status, treatment	Sig diff for women but not men or overall. Results for high compared to low education in women shown		0.76 (0.60 to 0.96) exc treatment 0.84 (0.65 to 1.08) inc treatment	X		X
Hall et al (2004) [162]	Western Australia	9,080	1982-2001 and 1991-2001	Age, sex, yr of diagnosis, marital status, indigenous status, histology, surgery, insurance status, hospital status, remoteness index, rural	5-year survival	---	1.07 (0.94 to 1.20) and 1.05 (0.93 to 1.20)			X
Hardy et al (2009) [163]	USA – I SEER area	83,101	1991-2002	Age, sex, race, standard therapy	5 year survival 19,519 early stage, 80,519 late stage	---	1.38 (1.10 to 1.71) early 1.09 (1.06 to 1.12) late	X		

Table 5.1 (cont). Summary of previous evidence from studies examining likelihood of survival by SEP (in most deprived [low SEP] compared to least deprived [high SEP] group), for lung cancer

						Univariable HR	Multivariable HR	low SEP associated with:		
Study	**Country**	**N**	**Years of Diagnosis**	**Confounders**	**Further information**	**HR (IMD=5)**	**HR (IMD=5)**	**Higher HR**	**Lower HR**	**No association**
Schrivers et al (1994) [164]	various				Review inc 3 studies					X
Yim et al (2012) [165]	Korea	261	1999-2002	Age, sex, stage, PS, family history, no of outpatient visits		1.25 (0.87 to 1.80)	1.46 (0.99 to 2.14)			X

Table 5.1b. Summary of previous evidence from studies examining the likelihood of survival by SEP (in most deprived compared to least deprived group), for lung cancer: relative survival

						Relative survival (RS)	low SEP associated with:		
Study	**Country**	**N**	**Years of Diagnosis**	**Confounders**	**Further information**		**Poorer RS**	**Better RS**	**No association**
Coleman et al(2004)	England and Wales	107,317	1996-1999	Age, sex	5 year relative survival Sig in men only	-1.4%(dep gap in men)	X (men)		X (women)
Rachet et al (2010)	England	303,422	1996-2006	Age, sex	1 year relative survival (2006 results shown)	-1.6%(dep gap in men) -3.1%(dep gap in women)	X		
Shack et al (2007)	Scotland	20,851	1996-2000	Age, sex	5 year relative survival Sig in men only	-1.6%(dep gap in men)	X (men)		X (women)

5.3 Other factors influencing survival

Local variation in cancer management such as access to specialist surgeons might affect survival (26). A review found that cancer mortality was lower when treated by a specialist surgeon or centre (166) but the poor quality of some of the studies included meant that the evidence was not conclusive and no consideration was given to outcome differences by age, sex or SEP. In contrast, a 2001 review found that, in the majority of studies it examined, surgeon volume or experience did not significantly affect colorectal cancer mortality (94). However, there is some more recent evidence to suggest that outcomes are better for colorectal patients who are managed by a specialist surgeon. The odds of death within 30-days post-operatively and within five-years were significantly lower for those managed by a specialist, taking into account age, sex, stage, SEP, tumour site and whether elective or emergency surgery was performed (167).

Breast cancer survival in the UK is lower than in other European countries with similar healthcare systems such as Norway and Sweden, possibly due to more advanced stage at presentation (168). Older patients also had poorer survival with a suggestion that they may be less likely to receive optimal treatment (168).

5.3.1 *Lung cancer*

Five-year survival for lung cancer is lower in England than in other European countries with similar healthcare systems, with a suggestion that this may be due to differences in management and access to treatment (169). A recent study found that lung cancer survival differences between six countries [including the UK] were partly due to differences in stage at diagnosis (170) but it was possible that some of the differences observed might also be due to problems with data quality and comparability, and to national differences in clinical decision making when dealing with borderline suitable patients such as older patients with poor PS and co-morbidities (170).

A study that simultaneously evaluated the management and survival of lung cancer patients in Teesside in the UK and in Varese in Northern Italy, two areas with similar lung cancer incidence, found that the resection rate was higher [24% compared to 7%], and three-year survival better [14% compared to 7%], in Italy compared to the UK

(171). The lower resection rate in the UK was ascribed to patients presenting with later stage cancer, having more aggressive tumours, and higher rates of co-morbidity. SEP and time interval delays were not measured, however.

A review examining the prognostic and predictive role of tumour type on survival found contradictory evidence, with some studies showing better survival for those diagnosed with adenocarcinoma and others suggesting more favourable outcomes for squamous cell cancers (19). Poor general health as measured by PS, but not the number of co-morbidities, was associated with poorer lung cancer survival (96) in a recent study. Better survival is found for those with good PS. In a study of 26,957 patients in Japan, the group with good PS [PS=0] contained the highest percentage of non-smokers and over half had stage 1 cancer (172). Smoking status was also found to be an independent prognostic factor for survival in this study, as were stage, sex and age (172). Women were shown to have better survival than men in a meta-analysis although the reasons for this are not clear. For early-stage survival it may be related to women being more likely to have a more slow-growing adenocarcinoma subtype. However, sex appeared to be an independent prognostic factor when stage, histology and smoking status were taken into account (173).

Age was shown to be strongly associated with early post-operative death [within 90 days of surgery], as was poor PS in a UK study using lung cancer audit data (174).

A study conducted using NYCRIS data did not find that increased travel time to hospital was associated with poorer survival, in fact the reverse (160).

There is a correlation between resection rates and survival (175). A recent UK study found that patients who were resident in trusts that had high surgical resection rates had reduced hazard of mortality compared to those with lower surgical rates, suggesting that survival rates could be improved if a higher proportion of patients were resected (161). The authors also suggest that as these rates were insensitive to adjustment for patient age and SEP then these associations were due to physician or hospital-level factors (176). Patients assessed by an MDT had better survival than those in a previous cohort, who were not (98).

5.4 Delay and survival

Does delay affect survival? The influence of patient and healthcare delay on cancer survival is unclear, according to one review (26). A scoping review identified 47 studies looking at 13 different cancers, of which 11 found a positive association, 9 a negative association and 29 no association between increased delay and poorer outcome (177). If survival is measured from diagnosis or surgery rather than from the onset of symptoms then there is a possibility of lead-time bias (178) and many studies on delay do not take this into account (177).

Diagnostic delay has been implicated as a factor that contributes to the poorer survival of UK cancer patients compared to the European average (99, 102). However, there have been some contradictory findings regarding the importance of delay on survival. In some cases it appears that those with shorter system delays may, in fact, have poorer survival. This has been termed the Waiting Time Paradox [WTP].

The WTP suggests that sicker people are referred more quickly and, as they are more ill, have shorter survival (179). A small study of colorectal cancer patients found that shorter diagnostic interval was associated with higher mortality, but this was only seen for those with obvious alarm symptoms and not found for those presenting with vague symptoms, although there were only 67 patients in this latter group (179). A 2013 Korean study found that a delay of greater than 12 weeks from diagnosis to curative surgery was associated with increased mortality for colorectal and breast cancer patients but not for lung or thyroid cancer (180), so that different effects may be seen depending on the specific cancer. However, another study found that an excess wait [>62 days from diagnosis to curative surgery] for breast cancer had no impact on survival (181) so that contradictory results are also found within cancer types.

Although some individual studies have shown an association between delay and colorectal cancer survival (79) others have not (113). A 2007 review could not reach a definitive conclusion as to whether diagnostic and therapeutic delay affected survival for colorectal cancer patients (178), although there appeared to be delay differences between colon and rectal cancer (178, 182). A weak degree of association was found between increased delay and improved survival [which again might support this ‘sicker quicker’ WTP theory], but not all the studies considered tumour stage. The review

authors also remarked on the scarcity of studies that included other confounding factors such as age, sex, SEP and co-morbidities (178). A different review found that delaying adjuvant chemotherapy for longer than 8 weeks was associated with poorer overall colorectal survival (131).

A systematic review of the influence of delay on breast cancer survival found that patients with treatment delay had poorer survival but this was not seen when stage at diagnosis was taken into account (183).

5.4.1 *Lung cancer*

No association between timely care and survival for lung cancer has been shown in two literature reviews, as both found the evidence inconclusive (184, 185). The most recent review found three studies where timely care was associated with better lung cancer survival, four that found the opposite and eight that found no association. No meta-analysis was carried out. The quality of the studies included was mixed and most did not adequately control for age, stage, histology and co-morbidity (185). The authors suggest that this lack of control for confounding factors is likely to account for why those with more timely care had poorer survival, in the studies that found this. However, a recent study looking at delays in diagnosis and treatment on survival in SCLC patients found that patients who were diagnosed earlier had a poorer prognosis that those diagnosed later and they were able to take into account age, sex, stage and PS (186).

5.5 Summary of chapters 3-5

From the narrative review of inequalities in receipt of treatment for a number of cancers, there is some evidence that receipt of treatment and time to treatment is socio-economically patterned and that this may impact on socio-economic inequalities in survival, but it is not clear cut. The evidence is mixed and there are contradictory findings both within and between cancer types. A number of studies look at 'cancer' but analysing combined cancers is likely to mask any between-cancer differences. Differences in tumour development and prognosis may account for some of the between-cancer differences in time to, and receipt of, treatment.

Even in studies that focus on a particular cancer, the quality of the studies and different confounders included make comparisons difficult. A 2007 study noted that socio-economic inequalities in co-morbidity, stage at diagnosis and receipt of treatment, factors that may be potential explanations for socio-economic inequalities in cancer survival, have not been well explored (137). The role that delay may play in survival is unclear. In time interval analyses there is a lack of consistency in definitions of delay intervals, and a lack of control for potentially important confounders.

5.5.1 *Lung cancer*

Socio-economic gradients in lung cancer survival are found in a number of studies but these gradients appear to be attenuated or eliminated in a clinical trial where participants received equal treatment and in some observational studies where receipt of treatment was included in the model. If access to treatment does influence survival it is important to investigate factors such as SEP that might influence whether treatment is received.

Further work is required to determine whether socio-economic inequalities in receipt of lung cancer care do occur, what factors may be influencing this, and what role treatment inequality and delay might play in survival inequality.

Having determined the gaps in knowledge regarding the evidence for inequalities in lung cancer treatment, time to diagnosis and treatment, and survival, both in the lack of research in these areas as well as the poor methodological quality of the studies that have been conducted, and the lack of synthesis of the evidence, suitable research aims and objectives were developed. These are detailed in chapter 6.

Chapter 6. Aims and Objectives

6.1 Development of aims and objectives

The initial narrative literature review identified that further work was required to determine whether socio-economic inequalities in receipt of, and time to, lung cancer are found; what factors may be influencing this; and what role inequalities in treatment and in the referral, diagnostic and treatment intervals might play in survival inequality. No systematic synthesis of the evidence for socio-economic inequalities in lung cancer treatment, time to diagnosis and treatment, or survival has previously been conducted.

6.2 Aims and objectives

The following aims and objectives were developed in order to fill the gaps in knowledge that had been identified, and to help determine whether IGIs in lung cancer care are found:

Aim:

- To determine if there are socio-economic inequalities in lung cancer care and, if so, to identify where on the pathway of care these inequalities might occur: looking at receipt of treatment; referral, diagnostic and treatment intervals; and survival

Objectives:

- To conduct a systematic review of the literature on socio-economic inequalities in receipt of treatment for lung cancer
- To link routine secondary data in order to identify where on the pathway of cancer care inequalities might occur for lung cancer; specifically to describe the relationship between SEP and:
    - receipt of treatment;
    - delay in referral, diagnosis and treatment;
    - survival;

  whilst also taking into account age, sex, cancer stage, performance status, presence of co-morbidities and other potential confounding factors

This thesis includes two areas of work: a systematic review and meta-analysis of the evidence from the published literature on socio-economic inequalities in receipt of lung cancer treatment; an analysis of secondary data examining socio-economic inequalities in receipt of, and time to, treatment, and survival, for lung cancer.

Chapter 7 details the systematic review and meta-analysis of socio-economic inequalities in lung cancer treatment.

Chapter 7. Systematic review and meta-analysis of socio-economic inequalities in receipt of lung cancer treatment

Summary

Background

Socio-economic inequalities in treatment may occur for some common cancers. Although the incidence and outcome of lung cancer varies with socio-economic position, it is not known whether socio-economic inequalities in treatment occur. A systematic review and meta-analysis of existing research on socio-economic inequalities in receipt of treatment for lung cancer was conducted to investigate this.

Methods

MEDLINE, EMBASE and Scopus were searched up to September 2012 for cohort studies of participants with a primary diagnosis of lung cancer [ICD10 C33 or C34], where the outcome was receipt of treatment (rates or odds of receiving treatment) and where the outcome was reported by a measure of socio-economic position.

Forty six papers met the inclusion criteria and 23 of these papers were eligible for meta-analysis.

Results

Socio-economic inequalities in receipt of lung cancer treatment were observed. Lower socio-economic position was associated with a reduced likelihood of receiving any treatment [OR=0.79 (95% CI 0.73 to 0.86), p<0.001], surgery [OR=0.68 (95% CI 0.63 to 0.75), p<0.001] and chemotherapy [OR=0.82 (95% CI 0.72 to 0.93), p<0.001], but not radiotherapy [OR = 0.99 (95% CI 0.86 to 1.14), p=0.89], for lung cancer. The association remained when stage was taken into account for receipt of surgery, and was found in both universal and non-universal health care systems.

Conclusions

Lung cancer patients living in more socio-economically deprived circumstances are less likely to receive any type of treatment, surgery and chemotherapy. These inequalities cannot be accounted for by socio-economic differences in stage at presentation or by

differences in health care system. Further investigation is required to determine the patient, tumour, clinician and system factors that may contribute to socio-economic inequalities in receipt of lung cancer treatment.

7.1 Background

Socio-economic inequalities in incidence of, and survival from, the majority of cancers have been reported (8, 9, 136). The evidence for socio-economic inequalities in cancer treatment was explored in chapter 3. Although a recent non-systematic review found some evidence for socio-economic inequalities in receipt of treatment for colorectal cancer (11) overall the evidence from studies included in my narrative review was inconclusive. Study quality was variable and many studies did not account for important confounders. However, despite the lack of conclusive evidence for socio-economic inequalities in cancer treatment it has been suggested that socio-economic differences in access to treatment might at least partially explain socio-economic differences in cancer survival (26).

Incidence of lung cancer is higher (8, 16), and survival poorer (136), in the most deprived patient groups. However, it is not known whether socio-economic inequalities in receipt of treatment exist for lung cancer and, if so, what contribution they make to overall socio-economic inequalities in outcome. In order to explore the first of these questions a systematic review and meta-analysis of cohort studies examining the association between socio-economic position (SEP) and receipt of lung cancer treatment was undertaken.

7.2 Review Objectives

The aim of this review was to summarise the existing literature and to assess the published evidence for socio-economic differentials in receipt of treatment for lung cancer.

7.3 Methods

A protocol [Appendix C-C1] was developed and systematic methods used to identify relevant studies, assess study eligibility for inclusion and evaluate study quality. The review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines (187) [see Appendix C-C2 for PRISMA checklist].

7.3.1 *Literature Search*

The online databases of MEDLINE and EMBASE were searched up to September 2012 to locate studies examining receipt of treatment for lung cancer reported by a measure of SEP. This researcher [LF] developed the search strategy, which was refined with the help of a medical librarian. Slightly different strategies were required for each database [for example MEDLINE recognises the MESH term Lung Neoplasms/ whereas EMBASE does not and uses Lung cancer/]. No language restriction was applied [see Appendix C C3 for full search strategies]. A search of Scopus uncovered no further papers. Additional studies were identified by reviewing the reference lists of all included studies and by using a forward citation search to identify more recent studies that had cited included studies. EndNote X5 software was used to manage the references.

7.3.2 *Study Eligibility*

Studies that met the following criteria were included in the review: primary, cohort studies of participants with a primary diagnosis of lung cancer [ICD10 C33 or C34] reported separately from other cancers; published in a peer-reviewed journal; where at least one reported outcome was receipt of treatment [measured by rates or odds of receiving treatment]; and where receipt of this outcome was reported by a measure of SEP. Any curative or palliative treatment for lung cancer including surgery, chemotherapy and radiotherapy was included.

Studies where SEP was included as a descriptive variable or potential confounder but where outcomes for receipt of treatment by SEP were not presented were not eligible for inclusion but the authors were contacted to determine whether relevant data were available that might allow for inclusion in the review.

Studies where multivariable analysis was conducted [and included control for a minimum of age and sex as confounders]; receipt of treatment was compared to not receiving treatment; odds ratios [ORs] and 95% confidence intervals of receipt of treatment in low [most deprived] compared to high [least deprived] SEP was calculated; and SEP was not further stratified by another variable, were considered suitable for inclusion in meta-analysis.

Acceptable measures of SEP were: area-based indices of deprivation [e.g. Index of Multiple Deprivation (IMD), Townsend Score, Carstairs Index]; and area or individual measures of income; poverty; or education level.

7.3.3 *Study selection and data extraction*

Papers obtained from the database searches were independently assessed by two researchers [LF and a fellow PhD student HW] in three phases: title, abstract and full paper screening.

Initial screening of titles was carried out to remove obviously irrelevant papers. However, from a preliminary scoping review by LF, the early pilot searches recovered studies that, although they conducted analyses of receipt of treatment stratified by SEP, did not always mention this in the abstract or title. Therefore, in the title search, any titles that referred to uptake or receipt of surgery, chemotherapy and radiotherapy for lung cancer were retained. Papers with titles that examined disparities in cancer survival/mortality were also included as further checking of the abstract was required to determine if inequalities in access to treatment were also examined.

Abstracts were then screened and a subset of studies selected for further review and the full article obtained. Abstracts that referred to socio-economic inequalities in receipt of treatment were retained. Others that referred to racial, ethnic, geographical, sex and age-related disparities in treatment as well as disparities by insurance type were also retained as often these papers also looked at SEP, even if this was not mentioned in the abstract. Papers that considered delay were not included. Nor were studies examining access to hospice care as although some papers were recovered that considered this type of care the search was not designed to pick up delay or hospice care. Therefore not all papers looking at this are likely to have been found and so there was a risk of presenting a selective rather than systematic analysis of these areas.

Papers that were not available through Medline or Embase were obtained from Google scholar. Six papers were obtained via Inter-library loans and two were accessed in paper format only from Newcastle University library.

Two researchers [LF and HW] independently assessed the selected full papers for eligibility according to the study-eligibility criteria. Any disagreements at any of the screening stages were resolved by discussion between the two researchers in the first instance and with a third reviewer [JA] if agreement could not be reached.

Data extraction was carried out by LF using an Access database pro-forma developed for this purpose. Data relating to study authors, journal, study design, year of study, data source, number of participants, years of diagnosis, measure of SEP, confounding variables included in the analysis [such as age, sex, stage, co-morbidities, cancer type/site, vital/performance status, marital status, smoking status, cancer network, health board, hospital, emergency or elective treatment, distance from hospital/travel time, ethnicity, insurance status], type of treatment received [any, surgery, chemotherapy, radiotherapy], statistical tests carries out, outcome measures [treatment rates or odds of treatment], comparator used, significance [p values], precision [confidence intervals], other variables that were significant; were recorded. Data extraction was double-checked by HW in a random sample of 10% of the included studies.

There is evidence to suggest that health-insurance status is an important factor relating to access to lung cancer care in countries such as the USA that rely on insurance-based health care systems (188). Insurance status is less relevant and rarely measured in most other countries. Therefore studies were grouped into three categories during analysis: those conducted in a universal healthcare system [UHCS], free at the point of access [similar to the UK]; those conducted in countries with primarily private insurance healthcare systems [non-UHCS, similar to the USA] (189) and those conducted in countries with social insurance healthcare systems [similar to many European countries]. No studies were identified that fell into the third category.

7.3.4 *Population definitions*

A number of papers included the same or overlapping study populations or used a regional study population that was also analysed in another paper as part of a national data-set. Some rules had to be derived in order to define patient populations, deal with study data that was being utilised by more than one paper and to choose data from the most suitable paper for inclusion.

A study population was defined as being determined by the geographical area, the source of the data and the time period of diagnosis. If two papers used data from the same source and time period then these were defined as fully over-lapping populations. If a study presented separate data for early and late stage patients these were regarded as separate populations. If a paper contained a regional population that was a subset of a paper containing a national population then these were classified as separate but over-lapping populations. If papers used populations from the same data source where there was only one year of overlapping data and a number of different years either side then these were defined as partially over-lapping study populations [substantially non-over-lapping]. Appendix C4 examines papers with over-lapping populations in more detail, with a breakdown of how the inclusion decisions were made.

Quality score was used to determine the most appropriate paper to choose for inclusion in the final meta-analysis.

7.3.5 *Quality*

A quality tool was used to divide eligible papers into six study quality categories with 1 being the lowest, and 6 the highest, quality [see Appendix C5]. Quality assessment was based on internal validity [for measures of SEP and outcome]; type of analysis conducted [multivariable or univariable]; population included [population-based or selective]; quality of reporting; and adjustment for relevant confounders. Quality assessment was carried out by LF and checked by HW.

7.3.5.1 *Existing study quality tools*

A number of existing tools potentially suitable for assessing cohort study quality were considered including the Cochrane Tool for Assessment of Risk of Bias (190); three other tools recommended by Cochrane Review Groups: the Jadad Scale, the Moncrief Scale and the Newcastle-Ottawa Scale (191); the Scottish Intercollegiate Guidelines Network [SIGN] methodology checklist for cohort studies (192); the EPHPP Quality Assessment Tool for Quantitative Studies (193); and The STROBE [Strengthening the Reporting of Observational Studies in Epidemiology] guidelines [a checklist of 22 items

that should be included in cohort studies] (194). Details of these tools are found in Appendix C6 with a discussion of the suitability of each.

In a systematic review it is necessary to examine the methodological quality, that is - the internal validity, of the primary studies. However, previous systematic reviews have used quality tools that defined quality in a number of different ways. Some quality scales look at internal validity [risk of bias] but also measure external validity and the quality of the reporting, which are not measures of bias within the study. Assessment of quality can therefore be sub-divided into a number of categories such as internal validity [including selection, confounding, statistical analysis and outcome], external validity and reporting.

If quality scores are employed then they can be used in a number of ways. It is possible to include all papers regardless of quality, include only high quality papers or include all but use quality to divide papers into sub-groups so that high and low quality papers are analysed separately. Quality can also be used as part of a narrative synthesis to help explain any differences found (195).

Having examined a number of potential tools and considered the different ways that quality could be utilised, a quality tool was developed for this review.

7.3.5.2 *Development of a quality tool for this review*

As none of the existing tools considered were entirely appropriate for the type of studies included in this review and, as has been done for previous reviews (185, 188), we devised a suitable tool, adapting and utilising aspects of other available tools. This approach has the benefit of producing a quality tool that is highly specific for the type of studies examined and there was good agreement between researchers when using the tool.

Quality in this systematic review was appraised using criteria adapted from existing quality tools [SIGN, EPHPP and STROBE guidelines].

In order to be considered for meta-analysis papers had to present adjusted odds ratios and report confidence intervals. A quality checklist was constructed with a screening question used to split papers into those potentially suitable for meta-analysis [adjusted ORs and CIs reported], and those suitable for narrative synthesis [meet inclusion

criteria but do not present adjusted ORs]. Then a 19-point scale that examined study quality under the following headings: internal validity [selection], external validity, quality of reporting of the study, and confounding; with a scoring system, was utilised. The scoring system was then used to further sub-divide studies into 6 quality categories [with 1 being the lowest, and 6 the highest, quality], with the final score determined by the type of population included, internal validity, reporting of the study and confounders included.

Cohort studies reporting only univariable analysis are of lower quality than those conducting multivariable analysis, in terms of their ability to control for confounding. However, it was decided to include those papers in the narrative analysis, with their overall lower quality taken into account. Initially Harvest Plot analysis was considered as a method for pictorially displaying the narrative findings, as the authors of this method have suggested that the Harvest Plot could be adapted so that, instead of looking at suitability of study design, quality can be used to distinguish studies of the same design (196). However, the initial Harvest Plot graphs produced were difficult to interpret and so it was decided against this approach for the narrative review.

7.3.6 Statistical analysis

Trends in receipt of treatment across SEP groups were assessed in the descriptive narrative analysis of all studies that met the inclusion criteria.

Meta-analysis of eligible studies was undertaken using Cochrane Collaboration Review Manager 5.1. Only studies reporting multivariable analysis [quality scores 3-6] were included in the meta-analysis. Natural logs of the ORs and their standard errors [SEs] were calculated for use in Forest plots. Random-effects meta-analysis of the odds of treatment in the lowest compared to the highest SEP group was conducted. Where a study reported the most deprived class as the comparator then reverse ORs were calculated. Studies that presented a single OR as either an OR for a one unit increase in deprivation score or incremental quintile increase in income were not included.

Subgroup analyses by treatment type and healthcare system were conducted. The I^2 statistic was used to examine heterogeneity. In meta-analyses where a 'substantial' percentage [previously defined as I^2 >50%] (197) of the variability appeared to be due

to the heterogeneity of the studies rather than to chance, further subgroup analyses by stage, histology and quality score were conducted, where appropriate, in order to examine potential sources of heterogeneity. A funnel plot was utilised to assess potential publication bias.

Multiple papers using the same or overlapping study data were included. Sensitivity analyses were conducted including all eligible papers and using different combinations of included-papers but only data from the better quality or more detailed paper in each overlapping study group were included in the final meta-analyses to ensure independence of results. Sensitivity meta-analyses [showing results including partially-overlapping populations, and fully-overlapping populations] are included in Appendix C7.

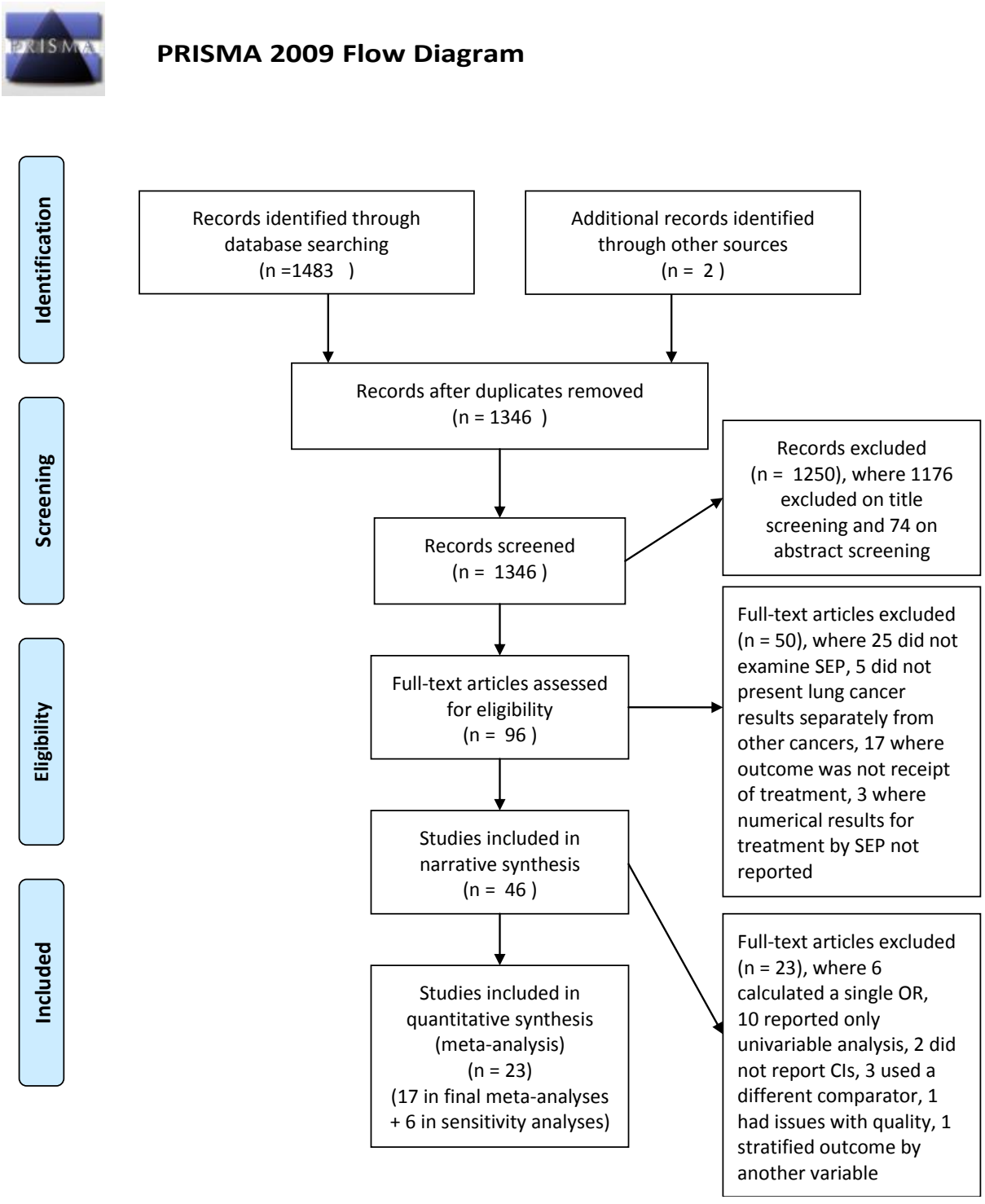
7.4 Results

7.4.1 *Included studies*

A total of 46 papers met the inclusion criteria and were included in the review [see Figure 7.1 PRISMA flow diagram].

Twenty eight papers were from UHCS countries [tables 7.1-7.2]. Of these, 19 UK papers examined 13 study populations, although as these included national and regional populations from different sources [cancer registries, Hospital Episode Statistics (HES) and lung cancer audit (LUCADA) data], there was some further population overlap. One UK paper also compared treatment in Scotland and Canada (198). A further nine papers from Canada [2], Sweden [1], Australia [1], Italy [1], France [1] and New Zealand [3] were included. The three New Zealand papers all examined the same population. These UHCS studies were published between 2001 and 2012, and examined populations diagnosed between 1986 and 2008.

Figure 7.1. Flow diagram of study selection and exclusion.



Abbreviations: SEP = socio-economic position, CI = confidence interval

Table 7.1. Characteristics of included studies potentially suitable for meta-analysis (universal health care systems).

									Confounders controlled for:					
Paper	**Country of study**	**Data Source (s)**	**Population included**	**Years of Diagnosis**	**Measure of SEP**	**No of SEP groups**	**Treatment given within**	**Age range**	**Age**	**Sex**	**Stage**	**Histology**	**Other**	**Quality score**
Berglund et al, 2010[73]	Sweden	Regional Lung Cancer Register (RLCR) - Sweden, Cause of Death Register and LISA (insurance and demographics)	Uppsala/ Orebro region in central Sweden	1996-2004	Education level (a)	3	NR	30+	Yes	Yes	Yes	Yes	Performance status, year of diagnosis, smoking status	6
Berglund et al, 2012[157]	England	Thames Cancer Registry, HES, LUCADA	South-east England	2006-2008	IMD 2007 income domain	5	NR	0-80+	Yes	Yes	Yes	Yes	Co-morbidity	6
Campbell et al, 2002[86]	Scotland	Scottish Cancer Registry and hospital case notes	Random sample from North/NE Scotland (with hospital record)	1995-1996	Carstairs Index	5	12 months	NR	Yes	Yes	Yes	Yes	Health board, distance to cancer centre, mode of admission	5
Crawford et al, 2009[199]	England	Northern and Yorkshire Cancer Registry and Information Service (NYCRIS)	Northern and Yorkshire region	1994-2002	IMD 2004 (access to services domain removed)	4	6 months	NR	Yes	Yes	No	Yes	Travel time (but overall results not stratified by travel time used here). Histology not included in receipt of any treatment analysis.	4
Erridge et al, 2002[200]	Scotland	Scottish Cancer Registry and medical records	Scotland (with hospital record)	1995	Carstairs Index	5	6 months	<60-80+	Yes	Yes	Yes	Yes	Health board (not inc in receipt of radiotherapy), diagnosis by specialist, management by oncologist	6
Erridge et al, 2009[198]	Scotland/ Canada	Scottish Cancer Registry and medical records; British Columbia Cancer Registry	Scotland/ British Columbia	1995	Carstairs Index/ average household income	2	6 months	<60-80+	Yes	Yes	Yes	Yes	Travel time, CT scan	4
Gregor et al, 2001[201]	Scotland	Scottish Cancer Registry and medical records	Scotland (with hospital record)	1995	Carstairs Index	5	6 months	<60-80+	Yes	Yes	Yes	Yes	Referral to specialist within 6 months of diagnosis	6

Table 7.1 (cont). Characteristics of included studies potentially suitable for meta-analysis (universal health care systems).

									Confounders controlled for:					
Paper	**Country of study**	**Data Source (s)**	**Population included**	**Years of Diagnosis**	**Measure of SEP**	**No of SEP groups**	**Treatment given within**	**Age range**	**Age**	**Sex**	**Stage**	**Histology**	**Other**	**Quality score**
Jack et al, 2003 [202]	England	Thames Cancer Registry	South-east England	1995-1999	Townsend (median score per health authority)	continuous (b)	NR	<35 - 85+	Yes	Yes	Yes	Yes	First hospital visited is a radiotherapy centre, basis of diagnosis, incidence. Health authority/hospital used as 2nd level in multi-level model.	4
Jack et al, 2006 [158]	England	Thames Cancer Registry and medical records	South-east London (with hospital record)	1998	IMD 2000	5	6 months	<55-85+	Yes	Yes	Yes	Yes	Consultant specialty, basis of diagnosis, (hospital, number of symptoms in some analyses)	6
Jones et al,2008[78]	England	Northern and Yorkshire Cancer Registry and Information Service (NYCRIS)	Northern and Yorkshire region	1994-2002	IMD 2004 (access to services domain removed)	continuous (c)	NR	NR	Yes	Yes	No	Yes	Travel time to hospital	4
Mahmud et al, 2003[203]	Ireland	National Cancer Registry of Ireland (NCRI)	Republic of Ireland	1994-1998	SAHRU area-based material deprivation index	3	6 months	15-80+	Yes	Yes	No	Yes	Health board, year of diagnosis	4/2(d)
McMahon et al, 2011[204]	England	Eastern Cancer Registry and Information Centre (ECRIC)	East of England	1995-2006	IMD 2004 (access to services domain removed)	5	NR	<60 - 80+	Yes	Yes	No	Yes	Year of diagnosis	4
Pollock &Vickers, 1998[76]	England	HES FCEs	North/South Thames (admitted to hospital)	1992-1995	Townsend	10	NR	<100	Yes	Yes	No	No	Hospital, mode of admission	3
Raine et al, 2010[77]	England	HES FCEs	England (admitted to hospital)	1999-2006	IMD	5	NR	50--90+	Yes	Yes	No	No	Trust, year of admission, mode of admission	3

Table 7.1 (cont). Characteristics of included studies potentially suitable for meta-analysis (universal health care systems).

									Confounders controlled for:					
Paper	**Country of study**	**Data Source (s)**	**Population included**	**Years of Diagnosis**	**Measure of SEP**	**No of SEP groups**	**Treatment given within**	**Age range**	**Age**	**Sex**	**Stage**	**Histology**	**Other**	**Quality score**
Riaz et al, 2012[161]	England	NCIN/UKACR cancer registries	England	2004-2006	IMD 2004	5	NR	0-- 85+	Yes	Yes	No	No	Government Office Region	4
Rich et al, 2011(1)[153]	England	LUCADA supplied by 157 NHS trusts	England	2004-2007	Townsend	5	NR	NR	Yes	Yes	Yes	Yes	Performance status. Adjusted for clustering by NHS trust	5
Rich et al, 2011(2)[152]	England	LUCADA and HES	England	2004-2008	Townsend	5	NR	30-100	Yes	Yes	Yes	Yes	Co-morbidity, ethnicity, surgery centre, radiotherapy centre, trial entry. Adjusted for clustering by NHS trust	5
Stevens et al, 2007[205]	New Zealand	Regional hospital and oncology databases checked against NZ cancer registry	Auckland-Northland region patients managed in secondary care	2004	NZ Deprivation Index	2	NR	<60-80+	Yes	Yes	Yes	Yes	Co-morbidity, private sector care, care discussed at MDM	3
Stevens et al, 2008[206]	New Zealand	Regional hospital and oncology databases checked against NZ cancer registry	Auckland-Northland region patients managed in secondary care	2004	NZ Deprivation Index	10	NR	<60-80+	Yes	Yes	Yes	Yes	Co-morbidity, private sector care, ethnicity	5

(a) Socio-economic index (SEI) and household income also measured but individual education level used in analyses as it contained least missing data

(b) Odds ratio for 1 unit increase in deprivation score, range unknown

(c) Odds ratio for 1 unit increase in deprivation score, range 1-80

(d) Quality score 4 where adjusted OR used and 2 where unadjusted rates used

Quality score ranges from 1 (lowest quality) to 6 (highest quality)

Abbreviations: HES = Hospital Episode Statistics, HES FCE= Hospital Episode Statistics Finished Consultant Episode, IMD = Index of Multiple Deprivation, LUCADA = Lung Cancer Audit, MDM = multi-disciplinary meeting, NCIN/UKACR = National Cancer Information Network/ UK Association of Cancer Registries, NR = not reported, OR = odds ratio, SEP = socio-economic position, UHCS=universal healthcare system

Table 7.2. Characteristics of included studies not suitable for meta-analysis (universal health care systems).

									Confounders controlled for:						
Paper	**Country of study**	**Data Source (s)**	**Population included**	**Years of Diagnosis**	**Measure of SEP**	**No of SEP groups**	**Treatment given within**	**Age range**	**Age**	**Sex**	**Stage**	**Histology**	**Other**	**Reason for exclusion**	**Quality score**
Battersby et al, 2004[207]	England	HES and East Anglian Cancer Intelligence Unit	17 PCTs in Norfolk, Suffolk and Cambridgeshire with HES record	1997-2000	IMD (weighted average for PCT)	NR	NR	NR	Yes	Yes	No	Yes	Incidence	Rate correlated against deprivation, by sex	1
Bendzsak et al, 2011[208]	Canada	Ontario Cancer Registry linked to CIHI hospital data, Insurance data and RPD database	Ontario	2003-2004	Neighbourhood income	5	12 months	20-75+	Yes	Yes	No	No	Univariable analysis	Univariable rate	2
Cartman et al, 2002[209]	England	Northern and Yorkshire Cancer Registry and Information Service (NYCRIS)	Yorkshire region	1986-1994	NR	NR	NR	<65-75+	Yes	Yes	No	Yes	Univariable analysis	Univariable rate	1
Hui et al, 2005[210]	Australia	NSW Central Cancer Registry and hospital records	Residents of 2 Area Health Services	1996	SEIFA-IRSD	5	NR	<50-70+	Yes	Yes	Yes	Yes	Univariable analysis	Univariable rate	2
Madelaine et al, 2002[211]	France	Manche Dept Cancer Registry	Manche	1997-1999	INSEE	4	NR	<54 - 75+	Yes	Yes	Yes	Yes	Urban/rural	Unemployed used as low SEP group and SEP group 2 used as baseline	2
Pagano et al, 2010[212]	Italy	Piedmont Cancer Registry of Turin	Turin	2000-2003	Education level	3	12 months	<65 - 75+	Yes	Yes	Yes	Yes	Marital status	Different comparator – *other* not *no* treatment	2

Table 7.2 (cont). Characteristics of included studies not suitable for meta-analysis (universal health care systems).

									Confounders controlled for:						
Paper	**Country of study**	**Data Source (s)**	**Population included**	**Years of Diagnosis**	**Measure of SEP**	**No of SEP groups**	**Treatment given within**	**Age range**	**Age**	**Sex**	**Stage**	**Histology**	**Other**	**Reason for exclusion**	**Quality score**
Patel et al, 2007[213]	England	Thames Cancer Registry	South-east England	1994-2003	IMD	5	6 months	0--100	Yes	Yes	Yes	Yes	Cancer network, year of diagnosis	Adjusted rates with no CIs. Possible errors in numbers.	2
Stevens et al, 2009[214]	New Zealand	Regional hospital and oncology databases checked against NZ cancer Registry listing	Auckland-Northland region patients managed in secondary care	2004	NZ Deprivation Index	10	NR	<60-80+	Yes	Yes	Yes	Yes	Univariable analysis	Univariable OR. Multivariable SEP results not shown	2
Younis et al, 2008[215]	Canada	Nova Scotia cancer registry and chart review	Nova Scotia	2005	Median household income	2	NR	65-75+	Yes	Yes	Yes	Yes	Co-morbidity, PS, hospital, surgery type, post-op complications, surgeon, med onc, education level, distance to cancer centre, marital status, smoking history	Univariable rate. Multivariable OR only for referral by SEP	2

Quality scores range from 1 (lowest quality) to 6 (highest quality)

Abbreviations: CI = confidence interval, HES = Hospital Episode Statistics, IMD = Index of Multiple Deprivation, NR = not reported, NSW = New South Wales, OR = odds ratio, PCT = Primary Care Trust, PS=performance status, SEIA-IRSD = Socio-economic Indexes for Areas - Index of Relative Social Disadvantage, SEP = socio-economic position, UHCS=universal healthcare system

Eighteen papers were from non-UHCSs – all of which were from the USA [tables 7.3-7.4]. The papers were published between 1995 and 2010 and examined populations diagnosed between 1978 and 2005. The majority of non-UHCS papers used sub-groups of the National Cancer Institute's Surveillance, Epidemiology and End Results [SEER] database population and, again, some population overlap was found. SEER has changed in size over the years. In earlier papers SEER covered 9, 10, and mostly 11 registries and included around 14% of the population but this increased to 16-17 registries and 26% of the population in later papers. Over half [11/18 = 61%] of the non-UHCS papers [7/10 in meta-analysis and 4/8 in narrative analysis] looked at receipt of treatment in a Medicare population aged over 65.

Twenty nine papers met the criteria for meta-analysis, 19 from UHCS (73, 76-78, 86, 152, 153, 157, 158, 161, 198-206) and 10 from non-UHCSs (216-225). However, six studies that examined receipt of treatment in more compared to less deprived SEP groups presented the results as a single OR [for a one unit increase or incremental quintile increase in deprivation score] and so could not be included in the meta-analyses. Seventeen studies were included in the final meta-analyses and a further six in the sensitivity meta-analyses.

Seventeen papers did not meet the criteria for meta-analysis and were excluded for the following reasons: Five studies did not conduct multivariable analysis and calculated only univariable rates (150, 208-210, 214). One paper calculated a rate of treatment by deprivation, stratified by sex (207). A further 11 papers were also excluded as, although they did include multivariable analysis, they stratified SEP by race (226), calculated but did not report adjusted rates by SEP, but did report univariable rates (71, 149, 227, 228), did not report confidence intervals (213, 229), had other quality problems (230), or used a different comparator (211, 212, 215).

In the study including Scottish and Canadian data (198) the numbers in some tables for the Scottish data did not appear to add up correctly. It was decided not to exclude this paper on quality grounds but to only include data from the Canadian cohort in the meta-analysis as this did not contain any apparent errors.

Table 7.3. Characteristics of included studies potentially suitable for meta-analysis (non-universal health care systems).

									Confounders controlled for:					
Paper	**Country of study**	**Data Source (s)**	**Population included**	**Years of Diagnosis**	**Measure of SEP**	**No of SEP groups**	**Treatment given within**	**Age range**	**Age**	**Sex**	**Stage**	**Histology**	**Other**	**Quality score**
Bradley et al, 2008[216]	USA	Michigan Cancer Registry and Michigan Medicare and Medicaid data	Medicare and Medicare/ Medicaid patients in Michigan	1997-2000	Census tract median household income (high v low)	2	6 months	66-80+	Yes	Yes	Yes	Yes	Co-morbidity, insurance type, ethnicity, urban/rural	4
Davidoff et al, 2010[217]	USA	SEER cancer registry linked to Medicare data	Medicare patients from 16 SEER registries	1997-2002	Census tract median household income	4	90 days	66-85+	Yes	Yes	Yes	Yes	Co-morbidity, performance status, ethnicity, marital status, rural/urban, prior Medicaid, tumour grade	5
Earle et al, 2000[218]	USA	SEER cancer registry linked to Medicare data	Medicare patients from 11 SEER registries	1991-1993	Census tract median household income(increase in OR per quintile)	5	4 months	65-104	Yes	Yes	Yes	Yes	Co-morbidity, year of diagnosis, ethnicity, rural/urban, teaching hospital, SEER area	5
Esnoala et al, 2008[219]	USA	South Carolina central cancer Registry linked to inpatient and outpatient surgery files	South Carolina	1996-2002	Income, zip code level (poverty/not living in poverty)	2	NR	<50-80+	Yes	Yes	Yes	Yes	Co-morbidity, year of diagnosis, insurance type, ethnicity, rural/urban, education, marital status, tumour location	4
Greenwald et al, 1998[220]	USA	SEER cancer registry	3 (Detroit, San Francisco, Seattle) out of 9 SEER registries	1978-1982	Census tract median household income (inc in OR per decile)	10	NR	<=75	Yes	Yes	Yes	Yes	Performance status, ethnicity	6
Hardy et al, 2009[221]	USA	SEER cancer registry linked to Medicare data	Medicare patients from 17 SEER registries	1991-2002	% individuals below poverty line at census tract level	4	NR	65- 85+	Yes	Yes	Yes	Yes	Co-morbidity, year of diagnosis, ethnicity, marital status, SEER area, other treatment	5
Hayman et al, 2007[222]	USA	SEER cancer registry linked to Medicare data	Medicare patients from 11 SEER registries	1991-1996	Census tract median household income	5	4 months/ 2 years	65- 85+	Yes	Yes	Yes	Yes	Co-morbidity, year of diagnosis, ethnicity, SEER area, hospitalisation, teaching hospital, distance to nearest RT centre, receipt of chemotherapy	5

Table 7.3 (cont). Characteristics of included studies potentially suitable for meta-analysis (non-universal health care systems).

									Confounders controlled for:					
Paper	**Country of study**	**Data Source (s)**	**Population included**	**Years of Diagnosis**	**Measure of SEP**	**No of SEP groups**	**Treatment given within**	**Age range**	**Age**	**Sex**	**Stage**	**Histology**	**Other**	**Quality score**
Lathan et al, 2008[223]	USA	SEER cancer registry linked to Medicare data	Medicare patients from 11 SEER registries	1991-1999	Census tract median household income (inc in OR per quintile)	5	NR	65+	Yes	Yes	Yes	Yes	Co-morbidity, ethnicity, SEER registry, urban, non-profit hospital, patient volume, % of black patients in hospital	5
Polednak, 2001[224]	USA	Connecticut Tumor Registry (SEER) and inpatient hospital discharge database (HDD)	Connecticut	1992 - 1997	Census tract poverty rate	5	NR	<55-80+	Yes	Yes	Yes	No	Co-morbidity, ethnicity, marital status	4
Smith et al, 1995[225]	USA	Virginia Cancer Registry and Medicare claims database	Medicare patients from Virginia cancer registry	1985-1989	Census tract: median household income by race and age	continuous (a)	6 months	65- 85+	Yes	Yes	Yes	Yes	Co-morbidity, ethnicity, county of residence, distance to oncologist	5

(a) Odds ratio for increase per $10,000 income

Quality scores range from 1 (lowest quality) to 6 (highest quality)

Abbreviations: CI = confidence interval, non –UHCS = non-universal healthcare system, NR = not reported, OR = odds ratio, SEER = National Cancer Institute's Surveillance, Epidemiology and End Results database, SEP = socio-economic position

Table 7.4. Characteristics of included studies not suitable for meta-analysis (non-universal health care systems).

									Confounders controlled for:						
Paper	**Country**	**Data Source (s)**	**Population included**	**Years of Diagnosis**	**Measure of SEP**	**No of SEP groups**	**Treatment given within**	**Age range**	**Age**	**Sex**	**Stage**	**Hist ology**	**Other**	**Reasons for exclusion**	**Quality score**
Bach et al, 1999[226]	USA	SEER cancer registry linked to Medicare data	Medicare patients from 10 SEER registries	1985-1993	Median income in zip code of residence (lowest quartile compared to highest 3)	2	NR	65-75+	Yes	Yes	Yes	Yes	Co-morbidity, ethnicity, SEER area	OR of surgery for black v white, univariable rates of surgery used here	2
Earle et al, 2002[227]	USA	SEER cancer registry linked to Medicare data	Medicare patients from 11 SEER registries	1991-1996	Census tract median household income	5	any time	NR	Yes	Yes	Yes	Yes	Co-morbidity, ethnicity, year of diagnosis, teaching hospital, seen by oncologist, SEER area	SEP non sig in multivariable analysis but only univariable rate shown.	2
Lathan et al, 2006[230]	USA	SEER cancer registry linked to Medicare data	Medicare patients from 11 SEER registries	1991-1999	Census tract median household income	5	NR	65+	Yes	Yes	Yes	Yes	Co-morbidity, ethnicity, SEER region, teaching hospital, rural/urban	Quality problems	2
Ou et al, 2008[149]	USA	California Cancer Registry (part of SEER)	California	1989-2003	Composite measure (7 indicators of education, income and occupation)	5	NR	0--89	Yes	Yes	Yes	Yes	Ethnicity, tumour grade, tumour location, histologic grade, marital status	SEP not reported in multivariable analysis. Univariable rate shown.	2
Suga et al, 2010[229]	USA	California Cancer Registry	Sacramento region in northern California	1994-2004	Census tract composite variable - income, education, employment, poverty, rent, housing value	5	NR	NR	Yes	Yes	Yes	Yes	Ethnicity, residence (urban/rural)	No CIs	2

Table 7.4 (cont). Characteristics of included studies not suitable for meta-analysis (non-universal health care systems).

									Confounders controlled for:						
Paper	**Country**	**Data Source (s)**	**Population included**	**Years of Diagnosis**	**Measure of SEP**	**No of SEP groups**	**Treatment given within**	**Age range**	**Age**	**Sex**	**Stage**	**Histology**	**Other**	**Reasons for exclusion**	**Quality score**
Tammemagi et al, 2004[71]	USA	Josephine Ford Cancer Center Tumor Registry	Detroit (receiving care at Henry Ford Health System)	1995-1998	Census tract median household income	continuous (a)	NR	NR	Yes	Yes	Yes	Yes	Co-morbidity, ethnicity, marital status, smoking history, alcohol use, drug use	SEP not reported in multivariable analysis. Univariable OR shown.	2
Wang et al, 2008[228]	USA	SEER cancer registry linked to Medicare data	Medicare patients 11 SEER registries	1992-2002	% below census tract poverty level	4	4 months	66-85	Yes	Yes	Yes	Yes	Co-morbidity, ethnicity, year of diagnosis, grade, SEER region, census tract education, marital status, teaching hospital, radiation	SEP not reported in multivariable analysis. OR for consultation but not treatment shown.	1
Yang et al, 2010[150]	USA	Florida Cancer registry linked to inpatient and outpatient medical records	Florida	1998-2002	Census tract poverty level	4	NR	<45-70+	Yes	Yes	Yes	Yes	Univariable analysis only	Univariable rate	2

(a) Odds ratio for increase per $10,000 income

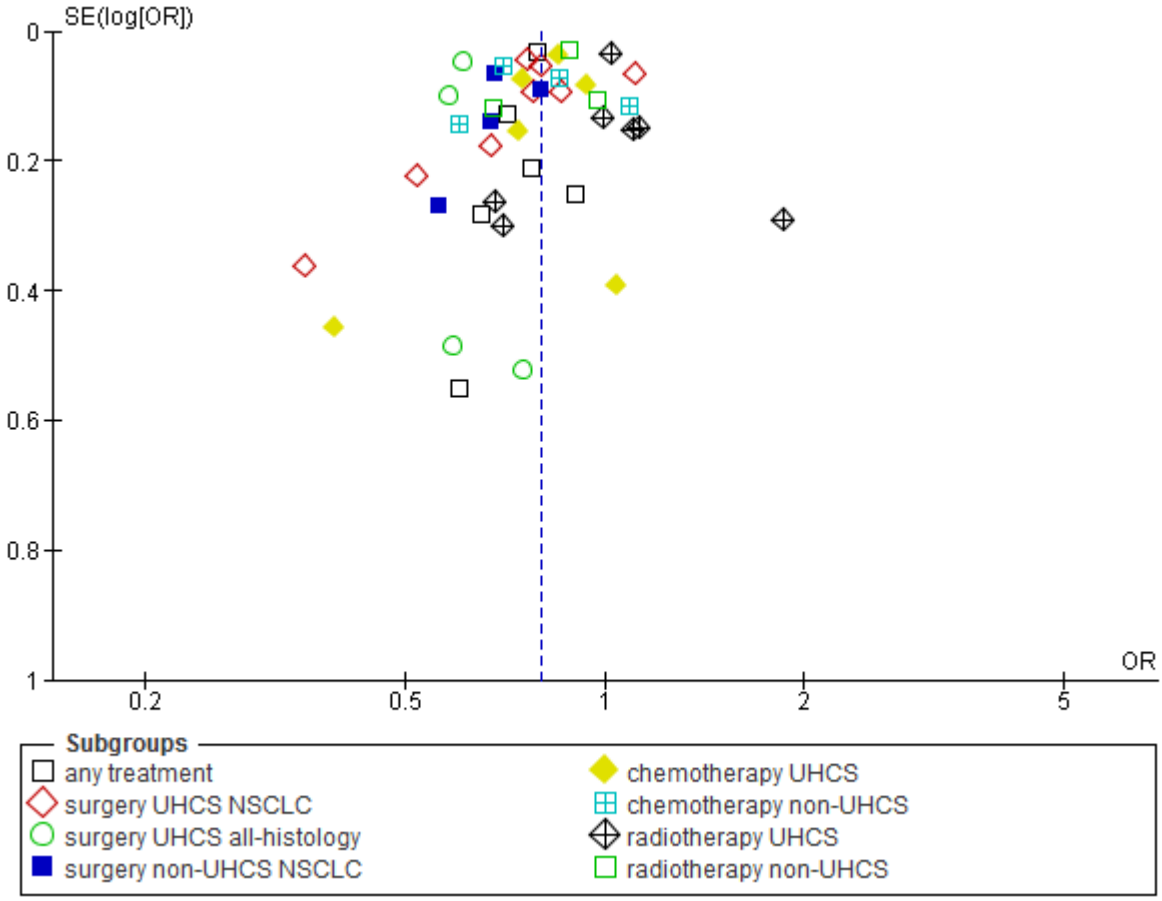
Quality scores range from 1 (lowest quality) to 6 (highest quality)

Abbreviations: CI = confidence interval, non-UHC S= non-universal healthcare system, NR = not reported, OR = odds ratio, SEER = National Cancer Institute's Surveillance, Epidemiology and End Results database, SEP = socio-economic position

A funnel plot to assess potential publication bias did not appear to show obvious bias [figure 7.2].

Individual measures of SEP were only available in one study (73) and SEP was otherwise measured throughout at an area-based level using a deprivation index, income, poverty or education level. The number of SEP groupings utilised varied from 2 to 10, and again this was taken into account in the quality scores.

Figure 7.2. Funnel plot to assess publication bias.



Abbreviations: non-UHCS = non universal health care system, NSCLC = non-small cell lung cancer, UHCS = universal health care system

7.4.2 *Quality Assessment of included studies*

Rates of treatment are not directly comparable between health care systems. Non-UHCS studies generally included NSCLC-patients only and used as the denominator only those patients eligible for treatment [e.g. stage I and II patients for surgery analyses]. Many also included details of co-morbidity. The SEER database only includes biopsy-confirmed cases of lung cancer and so systematically excludes those patients considered too old or unwell for biopsy [and therefore treatment]. UHCS papers rarely included co-morbidity, tended to look at rates of surgery for all lung cancers and did not stratify by stage.

In terms of quality the non-UHCS studies that carried out multivariable analysis had better control for confounding than UHCS studies, as they tended to stratify by stage and histology. However, half of the non-UHCS papers used a Medicare-only population where Medicare is a type of social insurance to which those aged over 65 are eligible. Non-UHCS studies are therefore less generalizable in population terms than the UHCS studies.

7.4.3 *Receipt of treatment*

7.4.3.1 *Surgery – overall analysis*

Thirty one papers [29 study populations] included receipt of surgery as an outcome, 18 UHCS papers [15 study populations] and 13 non-UHCS papers [14 study populations] [tables 7.5-7.6]. Of the papers that reported measures of significance [CIs or p-values], 20 out of 27 [74%] [64% of UHCS (9 /14) and 85% of non-UHCS (11/13) unique-population studies] reported that lower SEP was significantly associated with lower likelihood of surgery when comparing the lowest with the highest SEP group, although three of these 20 papers did not find a significant trend across groups. Seven papers found no significant association between SEP and receipt of surgery. Four papers did not report CIs or p values so were not considered here.

Table 7.5. Likelihood of receipt of surgery by SEP group (universal health care systems).

Study	No. receiving surgery	Cohort no./ no. eligible	Rate	Histology	OR/rate in Q1 (95% CI)	OR/rate in Q2 (95% CI)	OR/rate in Q3 (95% CI)	OR/rate in Q4 (95% CI)	OR/rate in Q5 (95% CI)	P value	Quality score	Meta-analysis	Further Information
Bendzsak et al, 2011[49]	1220	6499	18.77	any	21.1	18.3	19.7	18.8	16.8	0.02	2	N	Univariable rate
Campbell et al, 2002[35]	85	653	13.02	any	1.00	0.76 (0.28 to 2.09)	0.70 (0.27 to 1.84)	0.88 (0.35 to 2.22)	0.59 (0.23 to 1.53)	0.423	5	Y	P for trend
Hui et al, 2005[51]	NR	526		any	29	28	20	27	20	0.19	2	N	Univariable rate
Jack et al, 2003[39]	NR	32818		any					0.98 (0.95 to 1.01)	0.7759	4	N	
Jack et al, 2006[40]	42	695	6.04	any	1.00	0.82 (0.33 to 2.07)	0.89 (0.35 to 2.25)	0.16 (0.03 to 0.73)	0.75 (0.27 to 2.09)	0.1326	6	Y	Subset of Jack et al (2003) pop, p for trend
Jones et al,2008[41]	3552	34923	10.17	any					0.99 (0.99 to 1.00)	<0.01	4	N	
Pollock &Vickers, 1998[44]	2869	38668	7.42	any	1.00	0.83 (0.69 to 1.00)	0.73 (0.61 to 0.88)	0.82 (0.68 to 0.98)	0.58 (0.48 to 0.70)	<0.05	3	Y	Hospital population, p for trend
Raine et al, 2010[45]	8790	36902	23.82	any	1.63 (1.49 to 1.77)	1.58 (1.46 to 1.72)	1.45 (1.35 to 1.57)	1.34 (1.25 to 1.45)	1.00	<0.001	3	Y	Elective admission population
Raine et al, 2010[45]	8923	186741	4.78	any	5.5	5.2	4.8	4.4	4.5	NR	2	N	All admissions, univariable rate
Battersby et al, 2004[48]	387	4092	9.46	NSCLC					-0.10 (-0.55 to 0.40)	NR	1	N	Rate by sex correlated with deprivation score (men), with overall treatment rate
Battersby et al, 2004[48]				NSCLC					-0.16 (-0.59 to 0.35)	NR	1	N	Rate by sex correlated with deprivation score (women)
Berglund et al, 2010[19]	626	3369	18.58	NSCLC	1.93 (1.25 to 3.00)		1.33 (0.98 to 1.81)		1.00	NR	6	Y	
Berglund et al, 2010[19]	534	932	57.30	NSCLC	2.84 (1.40 to 5.79)		1.53 (1.01 to 2.31)		1.00	NR	6	Y(S)	Early stage only - stage IA-IIB
Berglund et al, 2012[22]	899	1826	49.18	NSCLC	1.00	0.74 (0.51 to 1.06)	0.71 (0.49 to 1.02)	0.73 (0.52 to 1.03)	0.67 (0.48 to 0.95)	0.29	6	Y	Early stage only – stage IA-IIB, p for trend
Cartman et al, 2002[50]	2401	12570	19.10	NSCLC	19.1				18.6	NR	1	N	Univariable rate

Table 7.5 (cont). Likelihood of receipt of surgery by SEP group (universal health care systems).

Study	No receiving surgery	Cohort no / no eligible	Rate	Histology	OR/rate in Q1 (95% CI)	OR/rate in Q2 (95% CI)	OR/rate in Q3 (95% CI)	OR/rate in Q4 (95% CI)	OR/rate in Q5 (95% CI)	P value	Quality score	Meta-analysis	Further Information
Crawford et al, 2009[36]	3335	18324	18.20	NSCLC	1.00	0.90 (0.81 to 1.00)		0.82 (0.74 to 0.91)	0.80 (0.72 to 0.89)	<0.05, <0.01, <0.01	4	Y	Individual P values reported
Mahmud et al, 2003[42]	866	4451	19.46	NSCLC	19.8		18.0		21.0	NR	2	N	Univariable rate
McMahon et al, 2011[43]	2374	18813	12.62	NSCLC	1.00	0.95 (0.83 to 1.09)	0.95 (0.83 to 1.08)	0.90 (0.79 to 1.03)	0.78 (0.65 to 0.94)	0.018	4	Y	P for trend
McMahon et al, 2011[43]									0.96 (0.93 to 0.99)	0.018		N	Paper presents results in 2 different ways
Riaz et al, 2012[34]	6900	77349	8.92	NSCLC	1.00	0.88 (0.80 to 0.96)	0.91 (0.83 to 0.99)	0.82 (0.76 to 0.89)	0.76 (0.70 to 0.83)	<0.01	4	Y(S)	P for trend
Rich et al, 2011(1)[46]	3427	24175	14.18	NSCLC	1.00	1.13 (0.98 to 1.32)	1.18 (1.02 to 1.37)	1.01 (0.87 to 1.16)	1.11 (0.96 to 1.27)	0.77	5	Y(S)	Subset of Rich et al 2011 (2) pop, p for trend
Rich et al, 2011(2)[21]	4481	34436	13.01	NSCLC	1.00	0.99 (0.88 to 1.11)	1.04 (0.92 to 1.19)	0.98 (0.84 to 1.13)	0.86 (0.71 to 1.04)	0.132	5	Y(S)	P for trend

Q1= high socio-economic position, Q5=low socio-economic position

Some studies reported SEP quintiles but others reported SEP in 2, 3 or 4 categories or as a continuous variable. Details of the number of SEP groups per study are given in Tables 1-4 in the column entitled 'No. of SEP groups'
Quality scores range from 1 (lowest quality) to 6 (highest quality)
Meta-analysis: Y=included in final meta-analysis, Y(S) = included in sensitivity meta-analysis, N=not included in meta-analysis

Abbreviations: CI = confidence interval, NR = not reported, OR = odds ratio, pop = population, SEP = socio-economic position , UHCS=universal healthcare system

Table 7.6. Likelihood of receipt of surgery by SEP group (non- universal health care systems).

Study	No. receiving surgery	Cohort no/ no eligible	Rate	Stage(s) included	Histology	OR/rate in Q1 (95% CI)	OR/rate in Q2 (95% CI)	OR/rate in Q3 (95% CI)	OR/rate in Q4 (95% CI)	OR/rate in Q5 (95% CI)	P value	Quality Score	Meta-analysis	Further Information
Bradley et al, 2008[57]	1336	2626	50.88	I,II,IIIa	NSCLC	1.00				0.80 (0.67 to 0.98)	<0.05	4	Y	
Esnoala et al, 2008[60]	NR	2791		local	NSCLC	1.00				0.67 (0.51 to 0.88)	0.005	4	Y	
Greenwald et al, 1998[61]	3053	5157	59.20	I	NSCLC					1.076	<0.0001	6	N	SE=0.011 (no CIs shown)
Hardy et al, 2009[62]	11834	19658	60.20	I,II	NSCLC	1.00	0.92 (0.84 to 1.14)		0.78 (0.75 to 1.03)	0.68 (0.60 to 0.77)	>0.05, >0.05, <0.05	5	Y	Individual p values reported corrected OR supplied[a]
Lathan et al, 2008[64]	4563	9688	47.10	I,II,III	NSCLC					1.06 (1.02 to 1.11)	NR	5	N	Subset of Lathan et al (2006) pop
Ou et al, 2008[70]	16185	19700	82.16	I	NSCLC	86.9	84.8	81.1	79.6	74.5	<0.001	2	N	
Smith et al, 1995[66]	801	2813	28.47	local	NSCLC					1.04 (0.90 to 1.19)	>0.001	5	N	
Tammemagi et al, 2004[72]	NR	1155		I,II	NSCLC					1.19 (1.03 to 1.30)	0.02	2	N	Univariable OR
Bach et al, 1999[67]	550	860	63.95	I,II	NSCLC	67.5				61.9	NR	2	N	Surgery (blacks)
Bach et al, 1999[67]	7763	10124	76.68	I,II	NSCLC	78.0				70.7	NR	2	N	Surgery (whites)
Polednak, 2001[65]	1385	1564	88.55	I,II	NSCLC	1.00	1.27 (0.74 to 2.18)	1.15 (0.65 to 2.03)	1.17 (0.67 to 2.04)	1.78 (1.05 to 3.01)	>0.05, >0.05, >0.05, <0.05	4	Y	Odds of **not** receiving surgery, individual p values reported
Smith et al, 1995[66]	57	2396	2.38	distant	NSCLC					1.27 (0.97 to 1.67)	>0.001	5	N	
Suga et al, 2010[71]	NR	12395			NSCLC					1.17	<0.001	2	N	Surgery after invasive staging, no CIs

Table 7.6 (cont). Likelihood of receipt of surgery by SEP group (non- universal health care systems).

Study	No. receiving surgery	Cohort no/ no eligible	Rate	Stage(s) included	Histology	OR/rate in Q1 (95% CI)	OR/rate in Q2 (95% CI)	OR/rate in Q3 (95% CI)	OR/rate in Q4 (95% CI)	OR/rate in Q5 (95% CI)	P value	Quality Score	Meta-analysis	Further Information
Suga et al, 2010[71]	NR	12395			NSCLC					1.18	<0.001	2	N	Surgery after non-invasive staging, no CIs
Lathan et al, 2006[69]	NR	14224			NSCLC					1.05 (1.02 to 1.08)	NR	2		
Yang et al, 2010[74]	NR	NR		all	all	24.6	22.2		20.7	18.3	<0.01	2		Univariable analysis

Q1= high socio-economic position, Q5=low socio-economic position

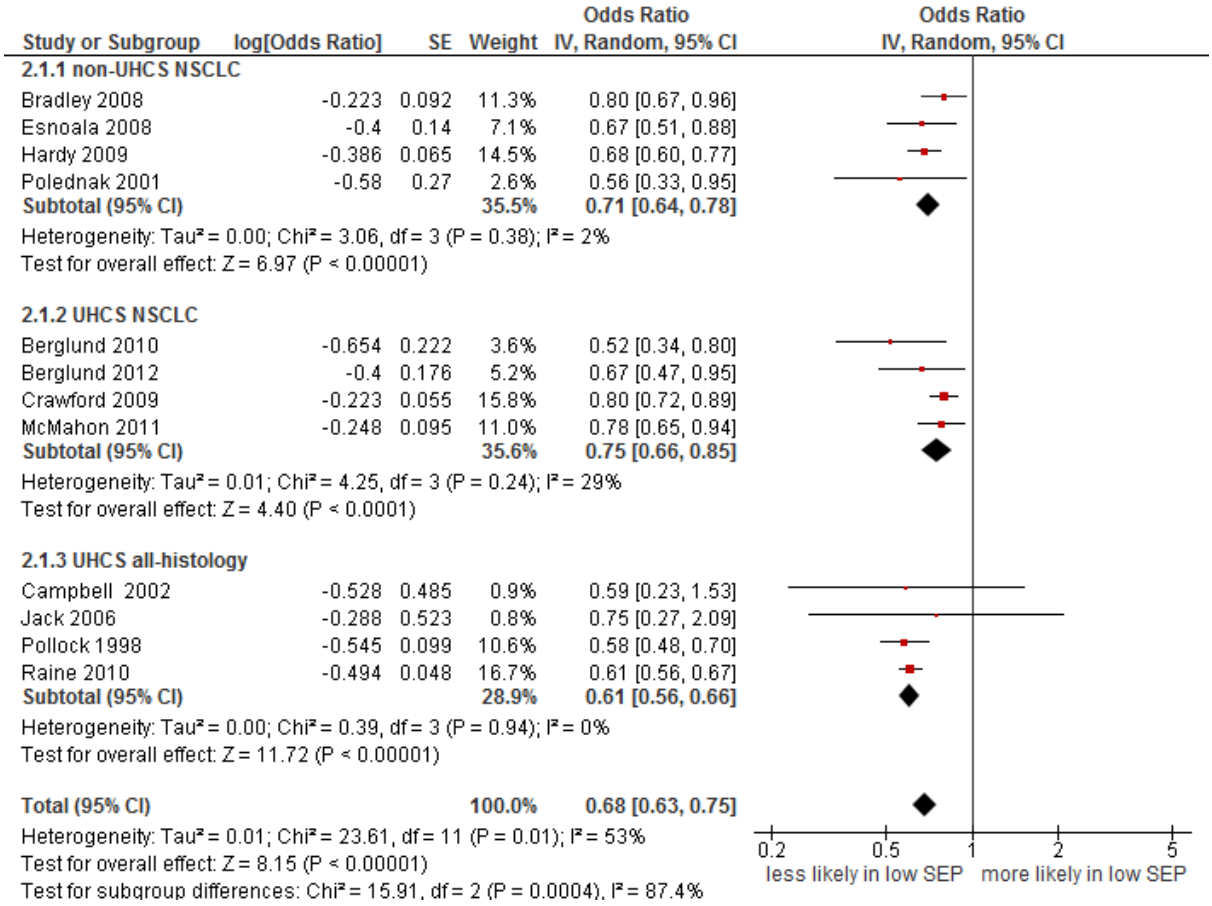
Some studies reported SEP quintiles but others reported SEP in 2, 3 or 4 categories or as a continuous variable. Details of the number of SEP groups per study are given in Tables 1-4 in the column entitled 'No. of SEP groups'
Quality scores range from 1 (lowest quality) to 6 (highest quality)
Meta-analysis: Y=included in final meta-analysis, Y(S) = included in sensitivity meta-analysis, N=not included in meta-analysis
a We are grateful to the authors for supplying a corrected OR to allow inclusion of this study in the meta-analysis

Abbreviations: CI = confidence interval, non –UHCS = non-universal healthcare system, NR = not reported, OR = odds ratio, pop = population, SE=standard error, SEP = socio-economic position

Meta-analysis of all 16 populations that were suitable for inclusion showed a significant negative effect of lower SEP on the likelihood of receiving surgery [OR=0.72 (95% CI 0.65 to 0.80) I^2=80%, p<0.001] [Appendix C, Fig C7.1]. Including only non-overlapping study populations [n=12] gave a similar result: [OR=0.68 (95% CI 0.63 to 0.75) I^2=53%, p<0.001] [Fig 7.3]. Similar results were also seen for the subgroup of 8 papers including NSCLC patients only: [OR=0.73 (95% CI 0.68 to 0.80) I^2=24%, p<0.001] [Appendix C, Fig C7.2] and with further stratification by health care system; NSCLC [UHCS]: [OR=0.75 (95% CI 0.66 to 0.85), I^2=29%, p<0.001]; NSCLC [non-UHCS, early stage only, co-morbidity included]: [OR=0.71 (95% CI 0.64 to 0.78) I^2=2%, p<0.001]; [Fig 7.3].

Lower SEP was associated with a lower likelihood of receiving lung cancer surgery, in both types of health care system, and in studies where histology and stage at diagnosis were taken into account.

Figure 7.3. Meta-analysis of odds of receipt of surgery in low (most deprived) versus high (least deprived) SEP.



Abbreviations: CI = confidence interval, non-UHCS = non universal health care system, NSCLC = non-small cell lung cancer, OR = odds ratio, SE=standard error, SEP = socio-economic position, UHCS = universal healthcare system

7.4.3.1.1 *Surgery - detailed analysis by healthcare system: UHCS*

Eight UHCS papers looked at receipt of surgery in any-histology populations [six registry studies (including two with overlapping populations) and two HES studies, so seven unique populations]. Rates of surgery varied from 4.8 to 18.8% [although a higher rate of 23.8% was seen for electively-admitted patients]. A significant association was seen between receipt of surgery and higher SEP in the HES studies [although neither of the two studies included stage or histology] but was seen in only one out of three non-overlapping multivariable-analysis registry studies [in the only study that did not include stage] and in one out of two univariable registry studies, although all studies showed trends in a reduction in OR as SEP decreased. Three of the studies where no association was found were very small [all less than 700 participants]. All of these studies included patients with SCLC who are rarely eligible for surgery.

Ten UHCS papers looked at receipt of surgery in NSCLC-only populations [seven registry studies, one HES and two audit studies]. Rates of surgery varied from 9.5 to 19.5% [although rates of 49.2% and 57.3% were seen for early stage patients]. All five multivariable-analysis registry studies found an association between lower SEP and reduced likelihood of receipt of surgery when comparing the lowest SEP group with the highest. Two studies looked at surgery for early stage patients only and both found higher odds of receiving surgery for patients in the highest SEP compared to the lowest but one did not find a significant trend across groups.

The other two univariable studies calculated rates not odds ratios and did not present p values. One study produced a correlated rate by sex. The two LUCADA papers using an overlapping study population did not find an association between SEP and receipt of surgery.

Similar meta-analysis results to those seen overall were found with stratification by health care system. Eight non-overlapping UHCS studies were suitable for inclusion, with an OR=0.67, 95% CI 0.54 to 0.77, I^2=65%, p<0.001, [with an OR=0.72, 95% CI 0.63 to 0.83, I^2=85%, p<0.001 when 12 over-lapping studies included], but again heterogeneity was high as these included studies that contained eligible NSCLC patients and some that also contained ineligible SCLC patients. Not all studies

accounted for stage. Including non-overlapping NSCLC-only UHCS studies [n=4] reduced the heterogeneity: [OR=0.75, 95% CI 0.66 to 0.85, I^2=29%, p<0.001] [fig 7.3].

In a subgroup analysis of the five partially-overlapping UHCS studies including stage [three studies that looked at NSCLC and two studies that looked at any-histology in registry and audit populations, all high quality studies, score 5 or 6] the association between lower SEP and reduced likelihood of surgery remained [OR=0.72, 95% CI 0.58 to 0.89, I^2=23%, p=0.002]. This was also found using any combination of non-overlapping studies.

In the four studies that did not conduct histology-specific analyses [two registry and two HES studies, where one HES study looked at receipt of surgery in electively admitted patients only] the summary statistic was OR=0.61, 95% CI 0.56 to 0.66, I^2=0%, p<0.001 [fig 7.3]. The two HES studies included only age and sex as confounders and so were of lower quality but accounted for over 98% of the weight in this meta-analysis.

7.4.3.1.2 *Surgery - detailed analysis by healthcare system: non-UHCS*

Ten US papers [11 populations] looked at receipt of surgery for early stage NSCLC. A significant association was seen between receipt of surgery and higher SEP in seven out of eight papers. However, in two of these studies the pattern across socio-economic groupings was not significant, only the OR in the lowest compared to the highest group was significant. A further 2 papers did not report CIs or p values. Rates of surgery varied from 28.5% to 88.6%.

Four studies compared the odds of surgery in the lowest compared to the highest SEP group. All four studies used different study populations and included co-morbidity as a confounder. The meta-analysis summary statistic was OR=0.71, 95% CI 0.64 to 0.78, I^2=2%, p<0.001; [Fig 7.3].

Table 7.7. Likelihood of receipt of chemotherapy by SEP group (universal health care systems).

Study	No receiving chemo	Cohort no/ no eligible	Rate	Histology	OR/rate in Q1 (95% CI)	OR/rate in Q2 (95% CI)	OR/rate in Q3 (95% CI)	OR/rate in Q4 (95% CI)	OR/rate in Q5 (95% CI)	P value	Quality Score	Meta-analysis	Further Information
Berglund et al, 2012[22]	3661	10039	36.47	any	1.00	0.90 (0.77 to 1.06)	0.78 (0.67 to 0.91)	0.77 (0.66 to 0.89)	0.75 (0.65 to 0.87)	<0.01	6	Y	NSCLC stage IIIA-IV & all stage SCLC, p for trend
Campbell et al, 2002[35]	124	653	18.99	any	1.00	0.58 (0.21 to 1.57)	0.72 (0.29 to 1.78)	0.41 (0.16 to 1.05)	0.39 (0.16 to 0.96)	0.028	5	Y	
Jack et al, 2003[39]	NR	32818		any					0.96 (0.94 to 0.98)	0.0001	4	N	Subset of Patel et al (2007) pop
Jack et al, 2006[40]	108	695	15.54	any	1.00	1.04 (0.50 to 2.16)	0.81 (0.38 to 1.70)	0.89 (0.43 to 1.85)	1.04 (0.48 to 2.25)	0.9130	6	Y	Subset of Patel et al (2007) pop, p for trend
Jones et al,2008[41]	5783	34923	16.56	any					0.99 (0.99 to 0.99)	<0.01	4	N	
Patel et al, 2007[54]	11217	67312	16.66	any	18.3	15.7	14.5	12.8	12.8	<0.001	2	N	Adjusted rates, no CIs
Rich et al, 2011(1)[46]	14168	59592	23.78	any	1.00	0.97 (0.90 to 1.04)	0.89 (0.83 to 0.96)	0.83 (0.77 to 0.89)	0.85 (0.79 to 0.91)	<0.01	5	Y(S)	
Hui et al, 2005[51]	NR	526		any	31	34	36	27	26	0.15	2	N	Univariable rate
Berglund et al, 2010[19]	1285	3369	38.14	NSCLC	1.35 (1.00 to 1.81)		1.25 (1.03 to 1.52)		1.00	NR	6	Y	
Pagano et al, 2010[53]	430	1231	34.93	NSCLC	1.00		0.98 (0.64 to 1.50)		1.63 (1.08 to 2.44)	NR	2	N	Odds of receiving chemo +/or radio rather than surgery
Younis et al, 2008[56]	29	108	26.85	NSCLC	4.7 (1.3 to 17.8)				1.0	0.015	2	N	Odds of referral for adjuvant chemo after surgery, stage I,II,III
Cartman et al, 2002[50]	1349	2448	55.11	SCLC	52.1				56.8	NR	1	N	Univariable rate
Crawford et al, 2009[36]	3619	5510	65.68	SCLC	1.00	1.10 (0.94 to 1.30)		0.91(0.78 to 1.08)	0.94 (0.80 to 1.11)	>0.05	4	Y	Individual p values, all reported as >0.05
Mahmud et al, 2003[42]	425	1002	42.42	SCLC	37.8		40.5		50.2	NR	2	N	Univariable rate

Q1= high socio-economic position, Q5=low socio-economic position

Some studies reported SEP quintiles but others reported SEP in 2, 3 or 4 categories or as a continuous variable. Details of the number of SEP groups per study are given in Tables 1-4 in the column entitled 'No. of SEP groups'

Quality scores range from 1 (lowest quality) to 6 (highest quality)

Meta-analysis: Y=included in final meta-analysis, Y(S) = included in sensitivity meta-analysis, N=not included in meta-analysis

Abbreviations: CI = confidence interval, NR = not reported, OR = odds ratio, pop = population, SEP = socio-economic position , UHCS=universal healthcare system

Table 7.8. Likelihood of receipt of chemotherapy by SEP group (non- universal health care systems).

Study	No receiving chemo	Cohort no/ no eligible	Rate	Stage	Histology	OR/rate in Q1 (95% CI)	OR/rate in Q2 (95% CI)	OR/rate in Q3 (95% CI)	OR/rate in Q4 (95% CI)	OR/rate in Q5 (95% CI)	P value	Quality Score	Meta-analysis	Further Information
Bradley et al, 2008[57]	643	2348	27.39	I,II,IIIa	NSCLC	1.00				1.09 (0.87 to 1.37)	>0.05	4	Y	
Hardy et al, 2009[62]	2951	19658	15.01	I,II	NSCLC	1.00	0.91 (0.81 to 1.02)		0.96 (0.85 to 1.09)	0.85 (0.74 to 0.98)	>0.05, >0.05, <0.05	5	Y	Individual p values reported
Ou et al, 2008[70]	1175	19700	5.96	I	NSCLC	5.3	5.7	5.3	6.9	7.4	0.001	2	N	Univariable analysis
Davidoff et al, 2010[58]	5499	21285	25.84	IIIB, IV	NSCLC	1.43 (1.28 to 1.60)	1.17 (1.05 to 1.30)		1.11 (1.00 to 1.22)	1.00	<0.01, <0.01, <0.05	5	Y	Individual p values reported
Earle et al, 2000[59]	1356	6308	21.50	IV	NSCLC					1.07 (1.02 to 1.12)	0.0077	5	N	Subset of Earle (2002)
Earle et al, 2002[68]	8813	12015	73.35	IV	NSCLC	41	41	36	31	27	>0.05	2	N	Univariable analysis only. SEP was included in multivariable analysis but non-sig (figs not reported)
Hardy et al, 2009[62]	26417	51243	51.55	III,IV	NSCLC	1.00	0.87 (0.78 to 0.96)		0.76 (0.63 to 0.90)	0.60 (0.45 to 0.79)	<0.05, <0.05, <0.05	5	Y(S)	Individual p values reported
Tammemagi et al, 2004[72]	NR	1155		III,IV	NSCLC					1.09 (1.01 to 1.18)	0.03	2	N	Univariable OR
Davidoff et al, 2010[58]	749	1946	38.49	IIIB, IV	NSCLC	0.86(0.69 to 1.08)	0.96 (0.77 to 1.19)		0.99 (0.81 to 1.22)	1.00	NR	5	N	Odds of single agent compared to doublet chemo.
Wang et al, 2008[73]	1521	3196	47.59	II,IIIa	NSCLC	1.00	1.08 (0.97 to 1.21)		1.08 (0.97 to 1.21)	0.97 (0.85 to 1.10)	NR	1	N	Odds of receiving oncology consultation.
Yang et al, 2010[74]	NR	NR		All	any	32.2	30.7		29.9	30.1	<0.01	2	N	Univariable analysis

Q1= high socio-economic position, Q5=low socio-economic position

Some studies reported SEP quintiles but others reported SEP in 2, 3 or 4 categories or as a continuous variable. Details of the number of SEP groups per study are given in Tables 1-4 in the column entitled 'No. of SEP groups'

Quality scores range from 1 (lowest quality) to 6 (highest quality)

Meta-analysis: Y=included in final meta-analysis, Y(S) = included in sensitivity meta-analysis, N=not included in meta-analysis

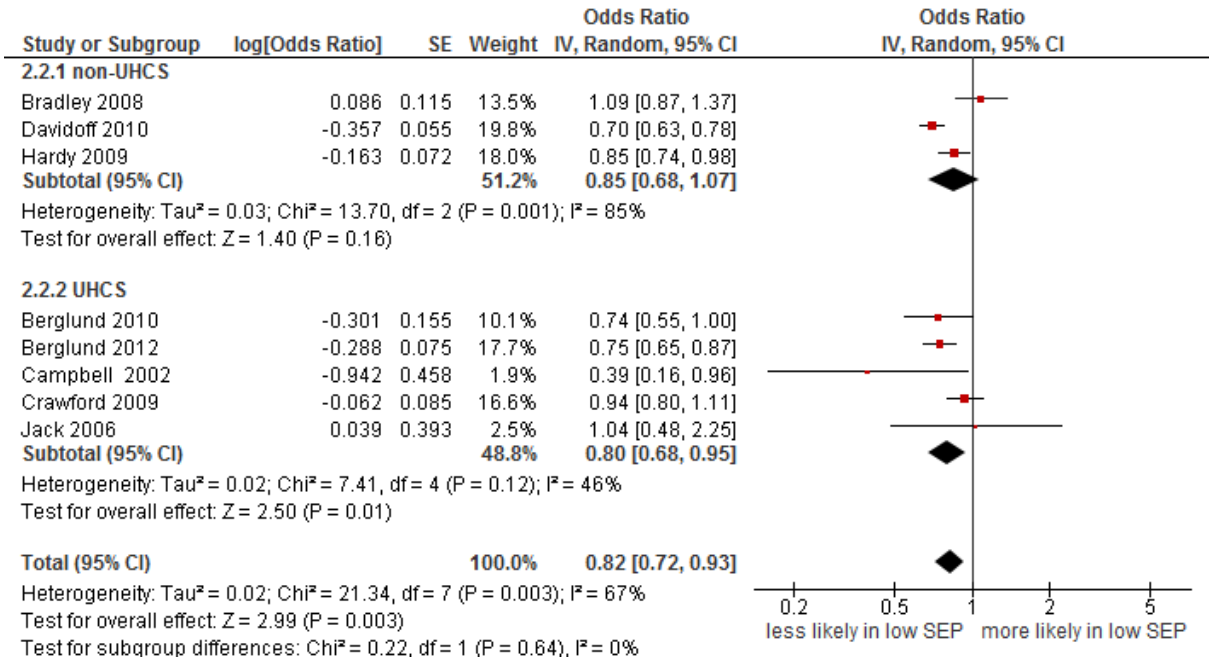
Abbreviations: CI = confidence interval, non –UHCS = non-universal healthcare system , NR = not reported, OR = odds ratio, pop = population, SEP = socio-economic position

7.4.3.2 Chemotherapy – overall analysis

Twenty three papers included chemotherapy as an outcome – 14 UHCS papers [12 populations] and nine non-UHCS papers [10 populations] [tables 7.7-7.8]. Of the 21 papers that reported measures of significance, 15 [71%] reported that lower SEP was significantly associated with lower likelihood of receipt of chemotherapy.

Meta-analysis of the ten populations that were suitable for inclusion found a significant negative effect of lower SEP on the likelihood of receiving chemotherapy: [OR=0.81, 95% CI 0.73 to 0.89, I^2=68%, p<0.001] [Appendix C, Fig C7.3]. Similarly, in a meta-analysis of the eight papers containing non-overlapping populations that were selected for inclusion, the odds of receiving chemotherapy were significantly lower for those in the most deprived SEP group compared to those in the least deprived [OR=0.82, 95% CI 0.72 to 0.93, I^2=67%, p=0.003], overall. A similar pattern was found in UHCS [OR = 0.80, 95% CI 0.68 to 0.95, I^2=46%, p=0.01]; and in non-UHCS settings [OR=0.85, 95% CI 0.68 to 1.07, I^2=85%, p=0.16], although this did not reach significance [Fig 7.4].

Figure 7.4. Meta-analysis of odds of receipt of chemotherapy in low (most deprived) versus high (least deprived) SEP.



Abbreviations: CI = confidence interval, non-UHCS = non universal health care system, OR = odds ratio, SE=standard error, SEP = socio-economic position, UHCS = universal healthcare system

7.4.3.2.1 Chemotherapy - detailed analysis by healthcare system: UHCS

Eight papers looked at receipt of chemotherapy in any-histology populations but three used overlapping populations. One paper included a NSCLC-only population. Rates of chemotherapy varied from 15.5% to 38.1% with the highest rate found in the paper including only a NSCLC population. Seven out of nine studies found an association between SEP and receipt of chemotherapy. Two small studies did not, one of which (158) was a subset of a population used in two larger studies where an association was seen (202, 231), and one which conducted only univariable analysis (210).

Three studies looked at receipt of chemotherapy in SCLC patients. Rates here varied from 42.4-65.7%. Two studies reported only univariable rates and no CIs but both showed a trend for increased rates of chemotherapy in more deprived groups. However, in the one study that conducted multivariable analysis no association between SEP and receipt of chemotherapy was found, although the trend was for reduced likelihood of chemotherapy in deprived populations, in contrast to the univariable studies.

In the meta-analysis five non-overlapping studies [three any histology, one NSCLC, one SCLC] reported OR for the lowest compared to the highest SEP group and a significant association between SEP and receipt of chemotherapy was seen [OR = 0.80, 95% CI 0.68 to 0.95, I^2=46%, p=0.005].

7.4.3.2.2 Chemotherapy - detailed analysis by healthcare system: non-UHCS

Eight non-UHCS papers looked at receipt of chemotherapy in 10 populations. One further study looked at the odds of receiving an oncology consultation but didn't report the odds of actually receiving treatment. Six out of 10 found an association between low SEP and lower likelihood of chemotherapy as a trend across SEP groups and one further study found an association only in the lowest SEP group compared to the highest.

Breaking this down further, eight studies looked at receipt of chemotherapy for NSCLC, three for early stage and five for late stage NSCLC. Two out of three early stage studies found an association between SEP and receipt of chemotherapy [where one included only univariable analysis and one where an association was seen only in the most

deprived group]. Only one out of five late stage studies did not find an association and this was in a univariable analysis (227). The same authors did find SEP to be significant in an earlier paper (218), with a significantly increased OR of receiving chemotherapy of 1.07, 95% CI 1.02 to 1.12, for each incremental quintile increase in SEP.

Three papers [four populations] were potentially eligible for meta-analysis, two had data on early stage and two on later stage. Including only the three non-overlapping populations gave a non-significant result [OR=0.85, 95% CI 0.68 to 1.07, I^2=85%, p=0.16].

In the two early-stage studies the results were contradictory. One study using Michigan registry data found non-significantly increased odds of receiving chemotherapy for lower-SEP patients (216) but a much larger study using SEER-linked Medicare data (221) found significantly reduced odds. When meta-analysis was conducted no association was found for SEP and receipt of chemotherapy [OR=0.95, 95% CI 0.74 to 1.21, I^2=70%, p=0.66]. However, heterogeneity was high and as both studies showed contradictory effects meta-analysis may not be suitable.

In the two studies that looked at late stage NSCLC and compared the odds of receiving chemotherapy in high and low SEP, the odds of receiving chemotherapy were significantly lower for those in the most deprived SEP group compared to those in the least deprived [OR=0.68, 95% CI 0.62 to 0.76, , I^2=2%, p<0.001]. Both these studies used Medicare-linked SEER data with some overlap in the study populations.

Table 7.9. Likelihood of receipt of radiotherapy by SEP group (universal health care systems).

Study	No receiving radio	Cohort no/ no eligible	Rate	Histology	OR/rate in Q1 (95% CI)	OR/rate in Q2 (95% CI)	OR/rate in Q3 (95% CI)	OR/rate in Q4 (95% CI)	OR/rate in Q5 (95% CI)	P value	Quality Score	Meta-analysis	Further Information
Berglund et al, 2012[22]	1054	2771	38.04	any	1.00	1.16 (0.88 to 1.54)	1.17 (0.90 to 1.53)	1.18 (0.91 to 1.53)	0.99 (0.77 to 1.29)	0.67	6	Y	Stage III only, p for trend
Campbell et al, 2002[35]	412	653	63.09	any	1,00	2.08 (1.11 to 3.91)	2.27 (1.24 to 4.16)	1.47 (0.83 to 2.60)	1.86 (1.05 to 3.28)	0.378	5	Y	P for trend
Jack et al, 2003[39]	NR	32818		any					1.00 (0.99 to 1.02)	0.2048	4	N	
Jack et al, 2006[40]	338	695	48.63	any	1.00	1.24 (0.76 to 2.02)	0.76 (0.46 to 1.26)	0.98 (0.60 to 1.59)	0.68 (0.41 to 1.14)	0.0978	6	Y	Subset of Jack et al (2003) pop, p for trend
Jones et al,2008[41]	13857	34923	39.68	any					0.99 (0.99 to 1.00)	<0.01	4	N	
Rich et al, 2011(1)[46]	12079	59592	20.27	any	1.00	1.08 (1.01 to 1.16)	1.12 (1.04 to 1.20)	1.12 (1.04 to 1.20)	1.02 (0.95 to 1.09)	0.80	5	Y(S)	P for trend
Hui et al, 2005[51]	NR	526		any	52	62	51	55	55	0.84	2	N	Univariable rate
Stevens et al, 2009[55]	222	555	40.00	any	1.0	0.8 (0.4 to 1.5)	0.6 (0.3 to 1.2)	0.9 (0.5 to 1.6)	0.7 (0.4 to 1.3)	>0.05	2	N	Hosp pop, univariable OR
Berglund et al, 2010[19]	863	3369	25.62	NSCLC	0.91 (0.67 to 1.22)		1.12 (0.93 to 1.36)		1.00	NR	6	Y	
Erridge et al, 2002[37]	824	3177	25.94	NSCLC/ unknown	1.00	0.94 (0.70 to 1.26)	1.04 (0.79 to 1.38)	1.33 (1.01 to 1.75)	1.13 (0.84 to 1.51)	0.10	6	Y	
Mahmud et al, 2003[42]	1265	4451	28.42	NSCLC	26.1		29.0		29.9	NR	2	N	Univariable rate
Cartman et al, 2002[50]	693	2448	28.31	SCLC	37.1				39.5	NR	1	N	Univariable rate

Q1= high socio-economic position, Q5=low socio-economic position

Some studies reported SEP quintiles but others reported SEP in 2, 3 or 4 categories or as a continuous variable. Details of the number of SEP groups per study are given in Tables 1-4 in the column entitled 'No. of SEP groups'

Quality scores range from 1 (lowest quality) to 6 (highest quality)

Meta-analysis: Y=included in final meta-analysis, Y(S) = included in sensitivity meta-analysis, N=not included in meta-analysis

Abbreviations: CI = confidence interval, NR = not reported, OR = odds ratio, pop = population, SEP = socio-economic position , UHCS=universal healthcare system

Table 7.10. Likelihood of receipt of radiotherapy by SEP group (non- universal health care systems).

Study	No receiving radio	Cohort no/ no eligible	Rate	Stage	Histology	OR/rate in Q1 (95% CI)	OR/rate in Q2 (95% CI)	OR/rate in Q3 (95% CI)	OR/rate in Q4 (95% CI)	OR/rate in Q5 (95% CI)	P value	Quality Score	Meta-analysis	Further information
Bradley et al, 2008[57]	950	2348	40.46	I,II,IIIa	NSCLC	1.00				0.97 (0.79 to 1.19)	>0.05	4	Y	
Ou et al, 2008[70]	2779	19700	14.11	I	NSCLC	11.7	12.6	14.7	16.5	16.6	<0.001	2	N	Univariable analysis
Smith et al, 1995[66]	1323	2813	47.03	local	NSCLC					0.95 (0.83 to 1.09)	>0.001	5	N	
Hardy et al, 2009[62]	43519	51243	84.93	III,IV	NSCLC	1.00	1.01 (0.96 to 1.07)		0.93 (0.88 to 0.99)	0.88 (0.82 to 0.93)	0.05, <0.05, <0.05	5	Y	Individual p values reported
Hayman et al, 2007[63]	6436	11084	58.07	IV	NSCLC	1.48 (1.17 to 1.87)	1.50 (1.17 to 1.91)	1.32 (1.01 to 1.72)	1.25 (0.93 to 1.69)	1.00	<0.001	5	Y(S)	
Smith et al, 1995[66]	1438	2396	60.02	distant	NSCLC					1.00 (0.90 to 1.12)	>0.001	5	N	
Yang et al, 2010[74]	NR	NR		??	any	32.0	32.1		31.4	33.1	0.02	2	N	Univariable analysis

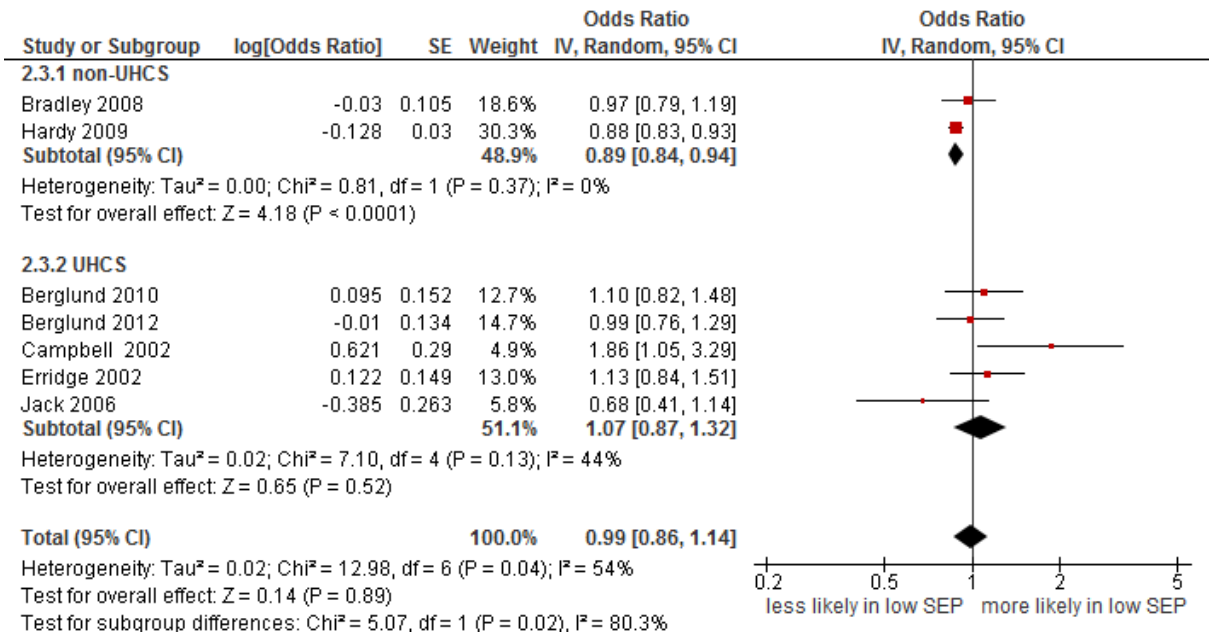
Q1= high socio-economic position, Q5=low socio-economic position
Some studies reported SEP quintiles but others reported SEP in 2, 3 or 4 categories or as a continuous variable. Details of the number of SEP groups per study are given in Tables 1-4 in the column entitled 'No. of SEP groups'
Quality scores range from 1 (lowest quality) to 6 (highest quality)
Meta-analysis: Y=included in final meta-analysis, Y(S) = included in sensitivity meta-analysis, N=not included in meta-analysis
Abbreviations: CI = confidence interval, non –UHCS = non-universal healthcare system , NR = not reported, OR = odds ratio, pop = population, SEP = socio-economic position

7.4.3.3 *Radiotherapy – overall analysis*

Eighteen papers [18 populations] examined receipt of radiotherapy for lung cancer - 12 in UHCS settings [11 populations] and six in non-UHCS settings [seven populations - six NSCLC-only populations and one study including any-histology] [tables 7.9-7.10]. Only one UHCS study found an association between SEP and receipt of radiotherapy. The non-UHCS studies had very heterogeneous outcomes.

Overall, no association between SEP and receipt of radiotherapy was seen in the meta-analysis of the seven studies with non-overlapping populations selected for inclusion [OR = 0.99, 95% CI 0.86 to 1.14, I^2=54%, p=0.89] [Fig 7.5], or when all nine studies were included [OR = 0.95, 95% CI 0.85 to 1.06, I^2=71%, p=0.40] [Appendix C, Fig C7.4]. A significant association was seen for non-UHCS studies but only two studies were included here, each looking at different stage patients.

Figure 7.5. Meta-analysis of odds of receipt of radiotherapy in low (most deprived) versus high (least deprived) SEP.



Abbreviations: CI = confidence interval, non-UHCS = non universal health care system, OR = odds ratio, SE=standard error, SEP = socio-economic position, UHCS = universal healthcare system

7.4.3.3.1 *Radiotherapy - detailed analysis by healthcare system: UHCS*

Eight papers using six registry populations [two with overlapping populations], one audit and one hospital-based population looked at receipt of radiotherapy for lung cancer in any-histology patients. A further three registry papers looked at NSCLC only and one at SCLC. Only one of these study populations reported an association between low SEP and reduced likelihood of receipt of radiotherapy and this study used SEP as a continuous variable, although the OR was very close to 1.00 [0.99] and the CI actually reached 1.00.

Five non-overlapping studies looked at the odds of radiotherapy in the lowest compared to the highest SEP quintile and the meta- analysis found no association [OR = 1.07, 95% CI 0.87 to 1.32].

7.4.3.3.2 *Radiotherapy - detailed analysis by healthcare system: non-UHCS*

Five non-UHCS NSCLC papers [including six populations] looked at receipt of radiotherapy, three for early stage and three for late stage NSCLC. One study examined an all-histology population. Two out of three late-stage studies found an association between low SEP and reduced likelihood of radiotherapy but one out of three early-stage [univariable analysis] study and one any-histology [also univariable analysis] study found an association between low SEP and increased likelihood of radiotherapy. Hence these are contradictory results. However, the univariable studies are of a low quality and look at rates of treatment rather than ORs.

7.4.3.4 *Surgery, chemotherapy and radiotherapy summary meta-analysis*

When the surgery, chemotherapy and radiotherapy papers included in the separate treatment meta-analyses in this systematic review were analysed together to produce an overall summary effect meta-analysis OR, low SEP was associated with a lower likelihood of receiving any type of treatment. This was found when including only studies with non-overlapping populations [OR = 0.79, 95% CI 0.73 to 0.86, I^2=77%, p<0.001] [Fig 7.6] and when including all eligible studies [OR = 0.80, 95% CI 0.75 to 0.86, I^2=82%, p<0.001] [Appendix C, Fig C7.5].

Figure 7.6. Meta-analysis of odds of receipt of any type of treatment in low (most deprived) versus high (least deprived) SEP (non- overlapping populations; n=31).

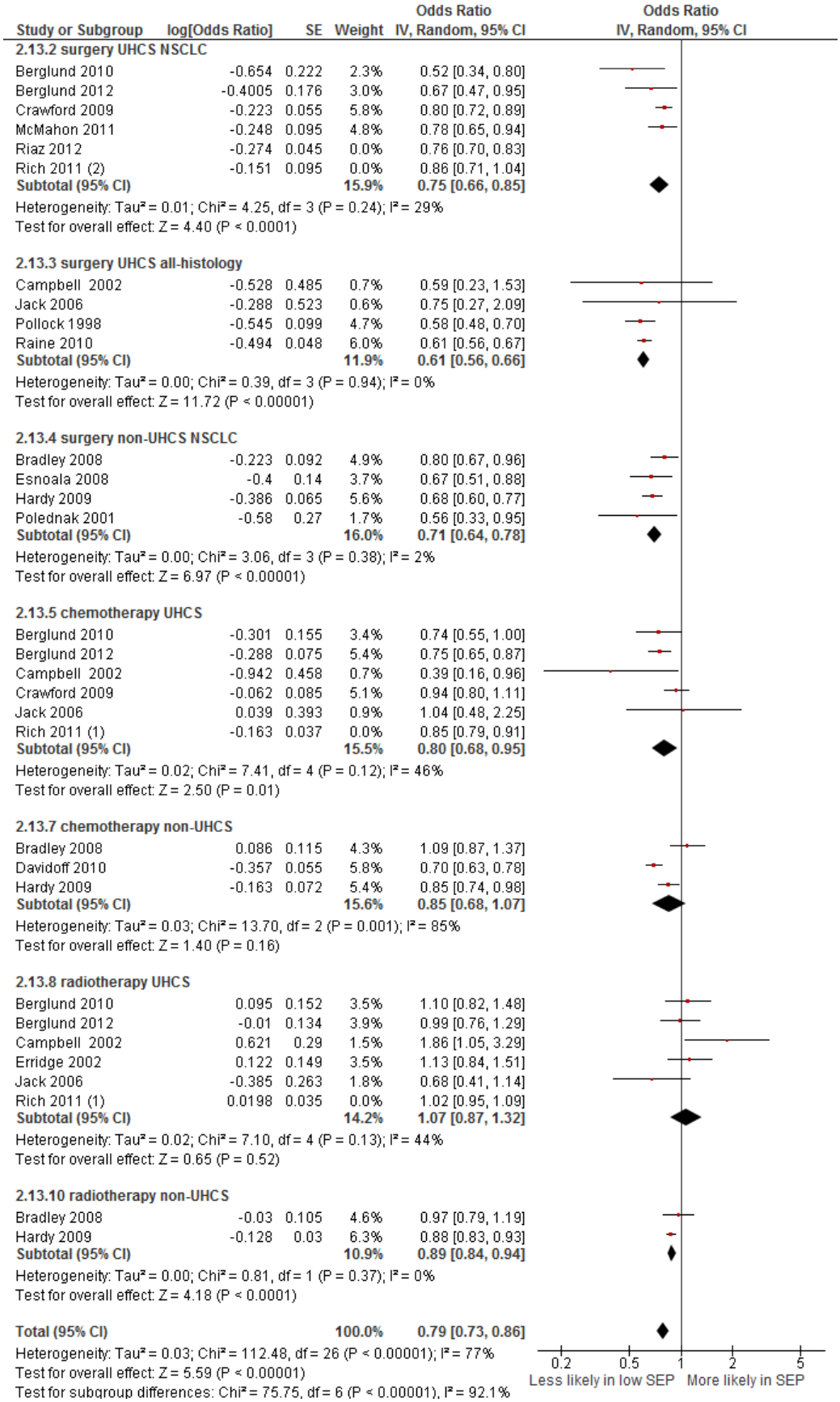


Table 7.11. Likelihood of receipt of any type of unspecified treatment by SEP group (universal health care systems).

Study	No. receiving treatment	Cohort no/ no eligible	Rate	Histology	OR/rate in Q1 (95% CI)	OR/rate in Q2 (95% CI)	OR/rate in Q3 (95% CI)	OR/rate in Q4 (95% CI)	OR/rate in Q5 (95% CI)	P value	Quality score	Meta-analysis	Further Information
Crawford et al, 2009[36]	19667	34923	56.32	any	1.00	0.91 (0.86 to 0.97)		0.82(0.77 to 0.88)	0.79 (0.74 to 0.84)	<0.01	4	Y	Individual P values, all reported as <0.01
Erridge et al, 2009[18]	2186	3833	57.03	any	1.3 (1.1 to 1.5)				1.00	<0.05	4	Y(S)	Scottish pop
Erridge et al, 2009[18]	1372	2073	66.18	any	1.3 (1.1 to 1.7)				1.00	<0.05	4	Y(S)	Canadian pop
Jack et al, 2003[39]	NR	32818		any					0.98 (0.96 to 0.99)	0.0091	4	N	
Jack et al, 2006[40]	414	695	59.57	any	1.00	0.91 (0.53 to 1.55)	0.69 (0.40 to 1.19)	0.57 (0.34 to 0.97)	0.65 (0.37 to 1.13)	0.03	6	Y	Subset of Jack et al (2003) pop, p for trend
Stevens et al, 2007[23]	285	565	50.44	any	1.0				0.9 (0.6 to 1.5)	0.773	3	Y(S)	Hospital pop
Mahmud et al, 2003[42]	2678	4451	60.17	NSCLC	1.0		0.9 (0.8 to 1.1)		1.0 (0.8 to 1.2)	0.39, 0.958	4	Y(S)	Odds of NOT receiving treatment – individual p values reported
Mahmud et al, 2003[42]	694	1002	69.26	SCLC	1.0		1.0 (0.6 to 1.5)		0.8 (0.5 to 1.3)	0.888, 0.358	4	Y(S)	Odds of NOT receiving treatment – individual p values reported

Q1= high socio-economic position, Q5=low socio-economic position
Some studies reported SEP quintiles but others reported SEP in 2, 3 or 4 categories or as a continuous variable. Details of the number of SEP groups per study are given in Tables 1-4 in the column entitled 'No. of SEP groups'
Quality scores range from 1 (lowest quality) to 6 (highest quality)
Meta-analysis: Y=included in final meta-analysis, Y(S) = included in sensitivity meta-analysis, N=not included in meta-analysis
Abbreviations: CI = confidence interval, NR = not reported, OR = odds ratio, pop = population, SEP = socio-economic position, UHCS=universal healthcare system

Table 7.12. Likelihood of receipt of any type of unspecified treatment by SEP group (non- universal health care systems).

Study	No. receiving treatment	Cohort no/ no eligible	Rate	Histology	OR/rate in Q1 (95% CI)	OR/rate in Q2 (95% CI)	OR/rate in Q3 (95% CI)	OR/rate in Q4 (95% CI)	OR/rate in Q5 (95% CI)	P value	Quality score	Meta-analysis	Further Information
Ou et al, 2008[70]	18216	19700	92.47	NSCLC	94.7	94.1	92.2	91.9	87.2	<0.001	2	N	Stage I. Univariable analysis
Smith et al, 1995[66]	1697	2396	70.83	NSCLC					1.00 (0.91 to 1.11)	>0.001	5	N	Distant stage
Smith et al, 1995[66]	2343	2813	83.29	NSCLC					1.00 (0.88 to 1.13)	>0.001	5	N	Local stage

Q1= high socio-economic position, Q5=low socio-economic position

Some studies reported SEP quintiles but others reported SEP in 2, 3 or 4 categories or as a continuous variable. Details of the number of SEP groups per study are given in Tables 1-4 in the column entitled 'No. of SEP groups'
Quality scores range from 1 (lowest quality) to 6 (highest quality)
Meta-analysis: Y=included in final meta-analysis, Y(S) = included in sensitivity meta-analysis, N=not included in meta-analysis

Abbreviations: CI = confidence interval, non –UHCS = non-universal healthcare system , NR = not reported, OR = odds ratio, pop = population, SEP = socio-economic position

Table 7.13. Likelihood of receipt of any type of unspecified curative treatment by SEP group (universal health care systems).

Study	No. receiving treatment	Cohort no/ no eligible	Rate/ eligible rate	Histology	OR/rate in Q1 (95% CI)	OR/rate in Q2 (95% CI)	OR/rate in Q3 (95% CI)	OR/rate in Q4 (95% CI)	OR/rate in Q5 (95% CI)	P value	Quality score	Meta-analysis	Further Information
Erridge et al, 2009[18]	548	3833	14.30	any	1.1(0.9 to 1.4)				1.00	>0.05	4	Y (S)	Scottish pop – subset of Gregor et al (2001) pop
Erridge et al, 2009[18]	546	2073	26.34	any	1.4(1.1 to 1.8)				1.00	<0.05	4	Y	Canadian pop
Gregor et al, 2001[38]	627	3855/ 1423	16.26/ 44.06	any	1.00	1.14 (0.72 to 1.80)	1.07 (0.69 to 1.66)	0.95 (0.62 to 1.47)	0.77 (0.51 to 1.16)	0.25	6	Y	Eligible = early stage
Stevens et al, 2008[47]	109	565	19.29	any	1.0	3.1 (1.0 to 9.7)	1.4 (0.4 to 4.4)	1.1 (0.4 to 0.3)	0.6 (0.2 to 1.8)	0.05, 0.60, 0.86, 0.40	5	Y	Hospital pop - subset of Stevens et al (2007) pop, individual P values reported

Q1= high socio-economic position, Q5=low socio-economic position

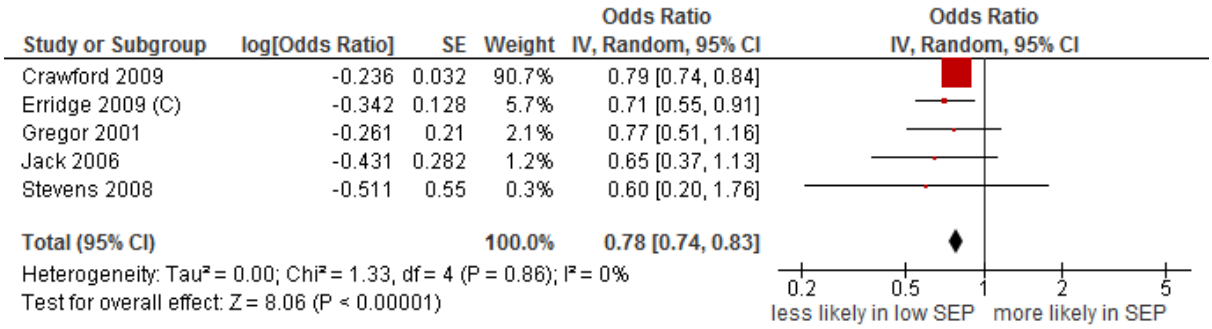
Some studies reported SEP quintiles but others reported SEP in 2, 3 or 4 categories or as a continuous variable. Details of the number of SEP groups per study are given in Tables 1-4 in the column entitled 'No. of SEP groups'
Quality scores range from 1 (lowest quality) to 6 (highest quality)
Meta-analysis: Y=included in final meta-analysis, Y(S) = included in sensitivity meta-analysis, N=not included in meta-analysis

Abbreviations: CI = confidence interval, NR = not reported, OR = odds ratio, pop = population, SEP = socio-economic position, UHCS=universal healthcare system

7.4.3.5 *Treatment type not specified – overall analysis*

Seven papers [eight study populations] examined receipt of unspecified treatment and three papers considered receipt of unspecified curative treatment in three populations [tables 7.11-7.13]. In the meta-analysis of five non-overlapping studies [all UHCS studies], low SEP was associated with a lower likelihood of receiving unspecified treatment [OR = 0.78, 95% CI 0.74 to 0.83, I^2=0, p<0.001] [Fig 7.7]. This was also seen when studies with overlapping populations were included [OR = 0.80, 95% CI 0.77 to 0.84, I^2=17%, p<0.001].

Figure 7.7. Meta-analysis of odds of receipt of unspecified treatment in low (most deprived) versus high (least deprived) SEP.



Abbreviations: CI = confidence interval, OR = odds ratio, SE=standard error, SEP = socio-economic position

7.4.3.5.1 *Treatment type not specified - detailed analysis by healthcare system: UHCS*

Five UHCS papers looked at receipt of any unspecified treatment [table 7.11] in six populations [although two contained overlapping populations]. All studies included any-histological-type and rates of treatment ranged from 50.4% to 66.2%. A significant association was seen between receipt of any treatment and SEP in four out of five non-overlapping populations, where those with lower SEP were less likely to receive any treatment. This association was not seen in one study that included a small hospital population.

Three UHCS papers also looked at receipt of any type of curative treatment [table 7.13] in a subset of the any-type-of-treatment populations. One study included a Scottish and Canadian population (198) and the Scottish population overlapped with that included in a second, better quality, study (201) hence three unique study populations

were examined. In only one out of three non-overlapping study populations was lower SEP associated with lower likelihood of any curative treatment.

Combining the any type of treatment and any type of curative treatment studies gave five non-overlapping populations suitable for meta-analysis. Low SEP was associated with a lower likelihood of receiving unspecified treatment [OR = 0.78, 95% CI 0.74 to 0.83, I^2=0, p<0.001] [Fig 7.7].

7.4.3.5.2 *Treatment type not specified - detailed analysis by healthcare system: non-UHCS*

Two studies looked at receipt of unspecified treatment for NSCLC in three populations using registry data from California and Virginia [table 7.12]. Rates of treatment ranged from 83.3% to 92.5% for early stage patients and 70.8% for late stage. A significant association was seen between receipt of unspecified treatment and SEP in one of the two studies, where those with lower SEP were less likely to receive any treatment. However, this was in an unadjusted analysis. In the study conducting multi-variable analysis no significant association was seen in either the early or late-stage population.

7.5 Discussion

7.5.1 *Principal findings*

To my knowledge, this is the first systematic review and meta-analysis examining socio-economic inequalities in receipt of lung cancer treatment. It showed an association between low SEP and reduced likelihood of receipt of any type of treatment, surgery and chemotherapy but not radiotherapy. The results were generally consistent across different health care systems.

7.5.2 *Interpretation of results*

Surgery is only suitable for early stage NSCLC patients and it has been suggested that cancer patients with lower SEP are more likely to present later and with later stage disease (108). This may help explain why socio-economic inequalities in receipt of surgery are observed in some studies. Therefore if stage is not included as a confounder then the absence of controlling for stage may account for some of the reduced likelihood of receipt of surgery in lower SEP groups. However, presentation

with later stage cancer in lower SEP patients has not been consistently observed (73). In this review, when receipt of treatment was examined in studies of early-stage patients only [from non-UHCS studies] and in UHCS studies where stage was taken into account, low SEP remained associated with reduced likelihood of surgery. Thus, the association between SEP and receipt of surgery appears to be independent of stage. Similar results were seen for NSCLC studies in both health care systems. If SCLC patients are included within the surgery denominator and histology is not controlled for, as greater levels of SCLC are seen in lower SEP groups due to smoking (17), this may be a valid reason for lower rates of surgery in this group.

Receipt of treatment may also be influenced by clinical suitability for treatment, and socio-economic differences in the number of co-morbidities present may explain socio-economic inequalities in treatment. In the three UHCS studies that took co-morbidity into account, SEP was not associated with receipt of surgery (152, 157) or of any treatment (205) when the trend across SEP groups was examined, suggesting that co-morbidity may be a potential mediator of socio-economic inequalities in treatment in UHCSs. However, most of the non-UHCS studies did include co-morbidity as a confounder and socio-economic inequalities in treatment were still observed, suggesting that there may be potential differences between healthcare systems in relation to the mediating effect of co-morbidity.

7.5.3 *Strengths and weaknesses of the review and of the available evidence*

This is one of the first equity reviews conducted (51, 61), the first systematic review of the literature on intervention-generated inequalities in lung cancer treatment, as well as the first cancer equity review to conduct meta-analysis. Extensive searches were carried out to identify studies. However, it is possible that not all relevant studies were obtained.

The included studies reported observational data only. The suitability of meta-analysis for observational studies has been questioned, as it may produce precise but spurious results (232). Examining the possible sources of heterogeneity by conducting sensitivity analyses across different sub-groups may be less prone to bias than calculating an overall summary effect (232). Here, although an overall summary effect OR was calculated, heterogeneity was taken into account. Separate analyses by type of

treatment were carried out, with further stratification by stage and histology. Universal and non-UHCSs were examined separately and random effects rather than fixed effects meta-analyses were conducted. These precautions did not change the overall pattern of results seen.

Significant heterogeneity remained in some cases, which could be considered as a limitation, although this is not surprising due to the characteristics of the studies included. For studies examining receipt of chemotherapy and radiotherapy it was generally not possible to differentiate between curative and palliative treatment and, if patterns of care differ for these by SEP, this might explain the high degree of heterogeneity seen. However, although there is some suggestion that heterogeneity can be considered high at >50% (197), when confidence intervals were calculated around the I^2 statistic these were wide, and so it was difficult to be confident about the degree of heterogeneity present (233).

Results for receipt of radiotherapy differed in the non-UHCS sub-group compared to overall but, as only two studies were included in this sub-group, it is difficult to be sure whether different patterns of receipt of radiotherapy by SEP are due to differences in healthcare system.

Many of the non-UHCS studies used over-lapping population sub-groups from the SEER database. There was also population overlap between some UHCS datasets. We attempted to include only substantially non-overlapping populations within the final meta-analyses to ensure independence of results. A judgement had to be made as to which was the best quality and most appropriate paper to include, but sensitivity analyses using different inclusion combinations [Appendix C, Fig C7.6] did not change the overall findings and nor did including all suitable studies regardless of population overlap [Appendix C, Figs C7.1, C7.3-C7.5].

Included papers contained data for patients diagnosed between 1978 and 2008. As treatment guidance has changed over time, older studies may be less applicable to current clinical practice. However, the majority of included studies were published within the last five years and sensitivity analyses excluding studies published prior to 2000 did not change the overall findings.

Various measures of SEP were utilised and these were categorised differently, which is an acknowledged problem in equity reviews (196). All but one study measured SEP at area-level. This is a further limitation, as area-based measures of SEP are unlikely to be accurate markers of individual-level circumstances and access to resources (234). Area-based measures of SEP can be calculated using address, making them easy to add to disease registers, such as those used in many of the studies synthesised here. However, the reliance on area-based markers of SEP may under-estimate the strength of the true association between SEP and receipt of treatment.

Not all studies reported details of stage and histology, both of which influence treatment type, and very few UHCS studies took co-morbidity into account. Thus, the ORs used in the meta-analyses were not consistently adjusted for the same covariates. However, I attempted to take these factors into account in the quality scores and by conducting subgroup sensitivity analyses. Examining only high quality studies did not alter findings nor did sensitivity analyses [for example, including only NSCLC studies or studies adjusting for stage], although consequent reduction in numbers did result in loss of significance in some analyses, potentially due to lack of power to detect differences.

In order to conduct meta-analysis it is necessary to compare the odds of treatment in the lowest SEP group with the odds in the highest, which simplifies what may be a complex relationship across SEP groups. However, studies that reported a change in odds ratios across the SEP categories and thus explored trends in receipt of treatment generally supported the overall findings of the review.

A number of existing tools suitable for assessing cohort study quality were considered (192, 194). However, none of these tools was entirely appropriate for the type of studies included and, as has been done in previous reviews (185, 188), we devised a unique tool, adapting and utilising aspects of other available tools. This approach has the benefit of producing a quality tool that is highly specific for the type of studies examined.

As with any systematic review, I was unable to exclude the possibility of publication bias. It was considered whether to search the grey literature including published abstracts, theses and reports from cancer registries and public health observatories,

but time and scope restraints prevented this. Studies reporting null findings are less likely to be published or, if they are published, not to report numerical outcomes (197). A funnel plot to assess potential publication bias did not appear to show obvious bias [Figure 7.2]. However, a number of papers recovered in the search included SEP in the description of the study population but did not report receipt of treatment by SEP (64, 161, 162, 235). Study authors were contacted and asked to provide further information, but only one supplied the requested data (161). It is likely that SEP was not significantly associated with receipt of treatment in the other studies but this was not always clearly reported. However, publication bias is thought to be less important than other sources of bias such as confounding, in meta-analyses of observational studies (232).

7.5.4 *Implications for policy and practice/ future research*

Socio-economic inequalities in receipt of treatment may exacerbate socio-economic inequalities in incidence of lung cancer, which is strongly associated with higher smoking rates in more deprived populations, and so may further contribute to the poorer outcomes in lower SEP groups.

Socio-economic inequalities in treatment may be due to differences in access to care. Within a non-UHCS it might be expected that socio-economic differences in receipt of treatment would be observed due to income-related differences in insurance status. Patients with lung cancer in the USA who do not have insurance have been reported to have more limited access to care (188). However, as socio-economic inequalities in receipt of lung cancer treatment were also observed in UHCS that do not depend on ability to pay, this would suggest that other system factors may be contributing to this inequality.

In non-UHCS, studies in younger populations, examining a range of insurance providers, are required.

The extent to which receipt of treatment is influenced by factors such as patient choice is not known. Variability at patient, tumour, system and individual clinician level needs to be investigated before clear recommendations for changes to policy and practice can be made. Further investigation into the factors that might contribute to socio-

economic inequalities in receipt of lung cancer care is necessary, to help develop interventions that ensure equitable receipt of appropriate treatment. This could include quantitative exploration of inequalities at each stage of the care pathway as well as qualitative work exploring reasons for inequality. It is likely that inequalities in receipt of treatment may contribute to inequalities in cancer survival and so cohort survival analyses are warranted in order to investigate intervention-generated inequalities in lung cancer outcomes.

7.6 Chapter summary

This review has demonstrated an association between lower SEP and reduced likelihood of receiving surgery, chemotherapy and any type of unspecified treatment, but not radiotherapy, for lung cancer.

If lower SEP patients are more likely to present with later stage cancer [although the evidence for this is unclear] they will be ineligible for surgery. Therefore if stage is not included as a confounder then the absence of controlling for stage may account for some of the reduced likelihood of receipt of surgery in lower SEP groups. Similarly, If SCLC patients are included within the surgery denominator and histology is not controlled for, as greater levels of SCLC are seen in lower SEP groups due to smoking (17), this may be a valid reason for lower rates of surgery in this group. Receipt of treatment may be influenced by clinical suitability for treatment, and socio-economic differences in the number of co-morbidities present may explain socio-economic inequalities in treatment. Better quality UHCS studies, including statistical control for co-morbidity, stage and histology, are required. Chapter 10 describes just such a study using a secondary linked data-set.

Chapter 8 now goes on to describe the data-set employed for the secondary data-analysis and an overview of the analytical methods.

Chapter 8. Exploring IGIs in lung cancer care using linked secondary data: Methods

8.1 Introduction

Socio-economic inequalities in receipt of surgery and chemotherapy for lung cancer were found in my systematic review and meta-analysis (236), as described in the previous chapter [chapter 7]. However, the quality of the included studies was mixed and many did not include important potential confounders such as stage, histology, PS and co-morbidity in the analyses.

To further investigate socio-economic inequalities in receipt of lung cancer treatment and the factors that might be influencing this, as well as exploring the role treatment inequality and delay might play in socio-economic inequalities in survival, Intervention-generated inequalities in lung cancer care in the North of England were explored using cancer registry [NYCRIS] data linked to Hospital Episode Statistics [HES] data and National Lung Cancer Audit [LUCADA] data. These linked secondary data sources were used to determine if there were socio-economic inequalities in lung cancer care and to identify where on the pathway of care these inequalities might occur – looking at time from GP referral to first hospital appointment, diagnosis and treatment; receipt of treatment; and survival. This chapter describes the methods employed to do this: the data sources used; variables included and the reasons for their inclusion; problems with data linkage and missing data; ethical approval; and an overview of the analytical methods.

Potential variables of interest, particularly those that had not previously been well explored, were determined from the literature and systematic reviews. An initial scoping exercise was then conducted to determine the availability and accessibility of data held by NYCRIS and HES that could be supplied in anonymised form. When it became clear that all variables of interest were not contained within these two datasets further linkage to the lung cancer audit dataset was considered. Tables A1-A3 in Appendix A show the variables that were included in the initial request and the reasons for their inclusion.

8.2 Data sources

The Northern and Yorkshire Cancer Registry and Information Centre [NYCRIS] is one of eight English regional cancer registries [11 in the UK] that collect a common minimum cancer dataset of information to obtain population-based figures for incidence of, and survival from, cancer. It covers a population of 6.6 million and registers approximately 50,000 incident cancer cases annually. Of these, around 5800 are lung cancer cases [2010 data] (237). From 1st April 2013 it became part of Public Health England.

The National Cancer Dataset uses data collected from all the registries. As well as their traditional registry role the registries also provide a cancer information and intelligence function. Validity and completeness of the data is also monitored. Active cancer treatments given within 6 months of diagnosis [surgery, chemotherapy, and radiotherapy] are well recorded in NYCRIS but not always so well recorded in other registries (237). Therefore, in order to look at adjuvant and palliative therapy as well as surgery, the investigative study uses NYCRIS regional, rather than national, lung cancer data.

Co-morbidity may be a factor determining whether treatment is offered (238) but details of co-morbidity are not collected by cancer registries. However, this data can be obtained from HES and used to calculate a co-morbidity score. Hospital Episode Statistics are stored in a HES 'data warehouse' containing details of all admissions to English NHS hospitals, and recording episodes of care from 1989 onwards. Other details of care including referring GP are also held in HES. The National Cancer Data Repository [NCDR] is a merged dataset of cancer registry data linked to an extract of HES (239).

Lack of stage data has been identified as a major limitation of cancer registry data (240). Definitive cancer staging requires extensive clinical investigation and levels of registry data on stage vary by cancer type. Lung cancer staging data is not routinely collected by cancer registries. However, the Lung Cancer Audit [LUCADA], a non-mandatory register of clinical information on patients diagnosed with lung cancer, does collect staging data. The audit initially included only a subset of registry patients whose data has been entered into LUCADA, which began in 2004. The audit examines the care delivered for patients diagnosed with lung cancer, and is run by The Health

and Social Care Information Centre in partnership with the Royal College of Physicians on behalf of the Healthcare Quality Improvement Partnership [HQIP].

8.3 Data

Data for patients with a primary diagnosis of lung cancer [ICD10 C33 and C34], diagnosed between 1997 and 2010 were requested from NYCRIS, and where linked data were available, with a linkage to HES [to supply co-morbidity score] and LUCADA [for stage and PS data]. The three data sources [NYCRIS cancer registry, HES and LUCADA data] were anonymised by NYCRIS and the three data-sets supplied by NYCRIS. The Thames Cancer Registry, the lead registry for lung cancer were contacted and they informed NYCRIS of the appropriate methods for linking, processing and extracting data from LUCADA, to ensure consistent rules were applied by NYCRIS. Records were allocated a unique randomly-generated key number, derived from the NHS number by NYCRIS, and the HES and LUCADA data were then linked by LF using this key.

8.3.1 *Data problems*

8.3.1.1 *Delays in obtaining data, and data linkage*

Registry data for patients diagnosed from 1997 to 2010 were supplied by NYCRIS in March 2012 but at that point it was still unclear whether HES and LUCADA data would be available. A national problem with the way that the co-morbidity score had been calculated meant that the data was withdrawn from use and NYCRIS were unclear about when this problem would be resolved. After much uncertainty the data eventually became available in November 2012. LUCADA data were obtained in December 2012. Data from HES and LUCADA were then imported and linked to the cleaned NYCRIS dataset.

8.3.1.2 *Data format*

When the initial registry data was received, in order to ensure that the data were non-identifiable I was not able to have access to the variable ‘date of death’. Instead survival time from date of diagnosis was calculated by NYCRIS. However, this was given in years, which was not appropriate for meaningful lung cancer survival analysis as

lung cancer has such a short survival period. After some negotiation it was agreed that survival time in weeks could be supplied. An estimated survival time in days could then be calculated with an accuracy of within 7 days of actual death. However, when the 'survival in weeks' variable did become available it was unfortunately not possible to append the new variable onto the existing dataset due to the way that the unique key for the dataset had been randomly generated by NYCRIS. Therefore a whole new un-cleaned dataset had to be sent by NYCRIS, meaning that all data cleaning and the generation of new variables had to be carried out again. Luckily as Stata 'do' files had been created for the initial data cleaning, this was not as big a set-back as it could have been.

8.3.1.3 *Missing data*

In the linked dataset the levels of stage, PS and co-morbidity data missing were high.

Inpatient HES data up until 31/3/2010 were theoretically available. However, although linked HES co-morbidity data were available for between 88.4% up to 92.0% of patients diagnosed between 1999 and 2008 [figures that are similar to those found in a similar study linking Thames cancer registry and HES data (157)], only 1.9% of those diagnosed in 2009 and 1.8% diagnosed in 2010 had a linked HES record [Appendix B]. National problems with the methodology used to calculate the co-morbidity score contained in the National Cancer Dataset meant that these all had to be re-calculated and so there was a resultant time-lag in their availability (NYCRIS, *personal communication*).

Stage and PS data were available from 2006 onwards. However, stage was only recorded for 27% of the 2006-2010 cohort, resulting in a large 'missing' category. Unfortunately the years in which the highest levels of stage and PS data were available [2009-2010] were also the years in which HES-linked data [and hence co-morbidity score] were not available for over 98% of the cohort. Patients diagnosed between 2006 and 2008 [n= 17,096] potentially had stage, PS and co-morbidity recorded although levels of stage data in these years were low and only 2080 had both details of stage and co-morbidity recorded. Those diagnosed between 1999 and 2005 had co-morbidity score but not stage or PS available.

The method for calculating date of diagnosis was changed in 2010 which might influence the comparability of the time intervals used in the time to diagnosis and treatment analyses for this year.

Some decisions therefore had to be made regarding which years of data to include in the analyses.

8.3.2 *Data-sets*

Data for patients with a primary diagnosis of lung cancer [ICD10 C33 and C34], diagnosed between 1997 and 2010 were initially requested from NYCRIS. However, patients diagnosed prior to 1999 did not have a valid IMD code and so could not be utilised.

Data for 66,891 patients with a primary diagnosis of lung cancer [ICD10 C33 and C34], diagnosed between 1st Jan 1999 and 31st December 2010, were available for use. Of these, 1681 had tumour registration based on death-certification only and so were excluded from analyses, leaving an eligible cohort of 65,210. 7776 [11.9%] had stage recorded in LUCADA [7769 in 2006-2010] and 51,614 [79.2%] had a HES linkage.

It was decided to split the cohort into two to best deal with missing data. Group 1 consisted of patients diagnosed between 1999 and 2005 [n=36,477], of whom 32,974 [90.3%] had a linked HES record. Stage and PS were not available. Patients diagnosed between 2006 and 2010 [n= 28,733] made up the 2nd group and, of these, only 18,650 [64.9%] had a linked HES record, 7769 [27.0%] had stage recorded in LUCADA and 8885 [30.9%] had a PS score. Analyses with and without the inclusion of co-morbidity were also conducted for group 2.

Multiple imputation for variables with missing data was considered but it is not recommended where over 50% of the data in a variable are missing (241). An alternative way to address the problem of missing data is to analyse only complete cases, although results from complete-case analyses can be biased (242). It was decided to analyse the full 2006-2010 dataset and include a 'stage missing' category and also to conduct a sub-group analysis of the 7769 staged-patients diagnosed in 2006-2010.

The distribution of each variable in the 1999-2005 and 2006-2010 subgroups and in the staged subgroup were compared to the overall cohort and to each other using the Chi squared (χ^2) test, to determine the representativeness of each of these groups.

Statistical analyses were performed using STATA v 12.0.

8.4 Data variables

8.4.1 *Registry data*

8.4.1.1 *Socio-demographic factors - SEP*

Socio-economic position [SEP] was calculated according to the agreed methodology for all English cancer registries, as the rank of the income domain of the Index of Multiple Deprivation [IMD], grouped into quintiles, based on the England-wide distribution of this variable.

IMD is an area-based composite measure of SEP and the UK government's preferred measure of deprivation. The English IMD provides a relative measure of deprivation at small area level across England. Areas are ranked from least deprived to most deprived, on seven different dimensions of deprivation as follows: income deprivation; employment deprivation; health deprivation and disability; education deprivation; crime deprivation; barriers to housing and services deprivation; and living environment deprivation (243). Postcodes of residence were used to assign individuals to small administrative areas known as lower-level super output areas [LSOA], containing an average of 1500 individuals.

To avoid any risk of including an indicator incorporating a health score, some studies have previously used the composite measure of IMD with the health domain removed (78, 199), but the agreed methodology for all English cancer registries is now to use only the income domain of the IMD and not to provide actual deprivation scores per LSOA, as scores are not a proportional measure of deprivation. An LSOA with a score of 40 is not twice as deprived as one with a score of 20 and so raw scores are not particularly meaningful (244). IMD is not directly comparable between England, Scotland and Wales as there are differences in sub-measures due to differences in rules for benefit qualification.

IMD quintiles were supplied by NYCRIS, where 5 is the most deprived and 1 the least deprived. The income domain of IMD 2010 was used for the most recent years of data, which is based on 2008 data and thus populations were derived from 2008 data for patients diagnosed between 2007 and 2010. For those diagnosed between 2003 and 2006 the income domain of IMD2007 was used [derived from 2005 data] and for 1999-2002 the income domain of IMD2004 [derived from 2001 data]. This changing-deprivation-score-over-time methodology was thought to be preferable to applying deprivation based on 2008 data back in time to much earlier years of diagnosis, as this may not properly reflect the deprivation of that area if, for example, there had been regeneration over the last decade (244).

Although data for patients diagnosed in 1997 and 1998 were available, valid IMD data were only available from 1999 onwards and so the records for the two earlier years were not used.

8.4.1.2 *Other socio-demographic factors*

Age at diagnosis was categorised into 4 groupings: age <60, 60-69, 70-79 and 80+ years.

Sex was categorised as M [male] and F [female].

Marital status is recorded by NYCRIS. This variable was requested but due to poor data completeness was not able to be supplied.

Data on ethnicity was supplied. However as ethnicity information was missing for 38% of the dataset and, of the 62% that had this variable coded, less than 1% of the dataset were characterised as non-white, this variable was not included in the final analyses.

As inequalities in receipt of treatment may have changed over time and to take into account the effect of the introduction of new guidelines for referral in 2005 (18), year of diagnosis was split into 4 categories: 1999-2001, 2002-2004, 2005-2007, 2008-2010. Individual years were utilised for the 1999-2005 and 2006-2010 datasets.

8.4.1.3 *Tumour factors*

There were 67 different cancer type codes listed in the registry dataset. Nine codes encompassed 96.1% of the records, relating to seven recognisable tumour types [table 8.1]. The remaining 3.9% had one of 58 different codes and these were classified as other-specified carcinomas.

Lung cancer was therefore categorised into eight morphological subtypes: adenocarcinoma, large cell carcinoma, non-small cell carcinoma, squamous cell carcinoma, small-cell carcinoma, other specified carcinoma [of which 26.6% were carcinoid tumours, codes M82413 and M82463], unspecified carcinoma (20) and neoplasm [table 8.1]. The neoplasm subtype included patients with a clinical diagnosis only.

Table 8.1. lung cancer histology and tumour type

Cancer code	Description	N	%	Tumour type	Histology
M81403	Adenocarcinoma unspecified	9,463	14.5	Adenocarcinoma	NSCLC
M80103	Carcinoma unspecified	4,615	7.1	Unspecified	Other
M80463	Non-small cell carcinoma	8,661	13.3	Non-small	NSCLC
M80123	Large cell carcinoma unspecified	2,140	3.3	Large cell	NSCLC
M80003	Neoplasm malignant	15,390	23.6	Neoplasm	Other
M80413	Small cell carcinoma unspecified	8,599	13.2	Small cell	SCLC
M80723	Squamous cell carcinoma non-keratinising	13,831	21.2	Squamous	NSCLC
M80723	Squamous cell carcinoma				NSCLC
M80713	Squamous cell carcinoma keratinising				NSCLC
	Other cancer type codes (n=54)	2,511	3.9	Other specified carcinomas	Other
Total		65,210	100		

Cancer type [histology] was classified as confirmed non-small cell lung cancer [NSCLC], including adenocarcinoma, large cell carcinoma, non-small cell carcinoma and squamous cell carcinoma subtypes; small cell lung cancer [SCLC]; and Other histology [including unspecified carcinoma, neoplasm, and other specified carcinomas (including carcinoid tumours)] [table 8.1].

When including only morphologically-specified lung cancers in analyses then the 'unspecified carcinoma/neoplasm' subtypes were excluded and the 'other specified carcinoma' subtype was included as probable NSCLC.

8.4.1.4 *Treatment*

The types of treatment [surgery, chemotherapy and radiotherapy] were used to derive a number of different treatment variables: three binary receipt of treatment variables - Surgery [y/n], Chemotherapy [y/n], Radiotherapy [y/n]; Type of First Treatment – categorised as surgery first, chemotherapy first, radiotherapy first, and no treatment; Types of Treatment – categorised as surgery, surgery + chemotherapy/radiotherapy, chemotherapy, chemotherapy + radiotherapy, radiotherapy, no treatment.

8.4.1.5 *Dates, interval periods and target times*

8.4.1.5.1 *Dates*

Dates of GP referral, first hospital appointment, diagnosis, and treatment received [surgery, chemotherapy and radiotherapy], were extracted from the cancer registry data.

For the 1999-2009 NYCRIS data, diagnosis date was determined by searching through case notes to collect information. Diagnosis date was determined as the first time the tumour was identified either by imaging or histology. From 2010 onwards UKACR guidance was followed. The guidance uses a priority hierarchy with 6 categories to determine date of diagnosis; the date of histological or cytological confirmation of malignancy [which can be derived from 3 different hierarchical time points]; then date of hospital admission; down to, with lowest priority, date of death if cancer is only identified at autopsy (100).

In order to calculate meaningful diagnostic and treatment intervals it is necessary to exclude those who have a diagnosis only after death. All death certificates that mention cancer are returned to the registry so that date of death can be recorded. If this cancer has not previously been entered on the register then further details are searched for retrospectively, but if medical records cannot be located then the cancer is registered as Death Certificate Only [DCO].These cases [n=1681] were excluded from analyses.

8.4.1.5.2 *Intervals and target times*

The following referral, diagnostic and treatment time intervals were potentially available for investigation:

Table 8.2. Referral, diagnostic and treatment intervals

Interval	Definition of interval	NCP* target time
Referral	GP referral date to first hospital appointment date	14
Diagnostic	*GP referral date to diagnosis date*	*31 (62-31)*
	first hospital appointment (FHA) date to diagnosis date	*17 (31-14)*
Treatment	diagnosis date to first treatment date	31
	GP referral date to first treatment	62

*National Cancer Plan

In England, three of these intervals have been the subject of performance management. Since 2000, urgent referrals for suspected cancer have been required to have a first hospital appointment [FHA] within 14 days from the date of referral [referral interval]. Since 2005, intervals of 62 days from date of urgent GP referral to first treatment and 31 days from diagnosis/decision to treat to first treatment [treatment intervals] have been in place (24). Interim time target periods [*italics*] can be inferred from these stated target times and calculated as follows: GP referral to diagnosis [62-31=31 days] and FHA to diagnosis [31-14=17 days].

Time from GP referral date to FHA was categorised as <=14 days [within target], >14 days, no referral interval recorded [either no GP referral date or no FHA date]. Time from GP referral date to treatment was categorised as <=62 days [within target], >62 days, no referral interval recorded [either no GP referral date or no FHA date]. Time from diagnosis to first treatment was categorised as: <=31 days [within target], 32-62 days, >62 days, no treatment.

8.4.2 *HES data – co-morbidity score*

Co-morbidities were derived from diagnostic codes in HES. A calculated co-morbidity score was then derived using the Charlson co-morbidity index, a validated instrument (245), and recorded in the National Cancer Registry Dataset. Only patients who had an inpatient episode with a condition that counted towards co-morbidity were included. Inpatient HES data up until 31/3/2010 were theoretically available.

A Charlson co-morbidity [CCM] score was calculated by NYCRIS using the number of inpatient HES admissions for 17 specified conditions [other than lung cancer] in the 3-18 months prior to diagnosis. Co-morbidities were assigned a weighted score [table 8.3] and the total score was the sum of weighted scores for the co-morbidities experienced.

No HES data linkage was available for 98.3% of patients diagnosed in 2009-10 as national problems in calculating the co-morbidity score meant that there was a time-lag in their availability. Patients without a CCM score were split into those who did and did not have a HES linkage. Those who had a linked HES record but no CCM score recorded on HES [CCM missing] were analysed separately from those who had no linked HES record and therefore no CCM score [no HES linkage].

CCM score was categorised as 0, 1-2, 3+, CCM missing, and no HES linkage.

Table 8.3. Calculation of Charlson co-morbidity (CCM) score

Charlson Group	Description	Charlson Score	Notes
1	Acute Myocardial Infarction	1	
2	Congestive Heart Failure	1	
3	Peripheral Vascular Disease	1	
4	Cerebral Vascular Accident	1	
5	Dementia	1	
6	Pulmonary Disease	1	
7	Connective Tissue Disorder	1	
8	Peptic Ulcer	1	
9	Diabetes	1	Only highest score is counted
10	Diabetes Complications	2	
11	Paraplegia	2	
12	Renal Disease	2	
13	Cancer	2	Derived from cancer registry data rather than HES data.
14	Metastatic Cancer	N/A	
17	Liver Disease	1	Only highest score is counted
15	Severe Liver Disease	3	
16	HIV	6	

8.4.3 *LUCADA data – stage and PS*

Lung cancer staging data is very poorly recorded in NYCRIS. Stage and performance status were therefore obtained from LUCADA records. These variables were only substantially available for patients who were diagnosed between 2006 and 2010.

The audit includes only a subset of registry patients whose data has been entered into LUCADA, which began in late 2004. Nationally, the percentage completeness varies

from only 40% for those diagnosed in 2005, with gradual increases over the years [66% in 2006, 75% in 2007, 85% in 2008, 95% in 2009, 93% in 2010 and 93% in 2011] (246). The number with stage recorded was also initially low [55% in 2006, although this is 55% of the 66% included so is only around 36.3% of the full number diagnosed that year] but again is increasing over time [85% in 2010, equivalent to 79% of all those diagnosed]. For my linked NYCRIS dataset the numbers were lower than this. Stage was recorded for only 11.8% in 2006 and increased to 63.1% in 2010 [see Appendix B].

Stage was assigned using the TNM staging system and categorised as I [IA,IB], II [IIA,IIB], III [IIIA,IIIB], IV and missing/uncertain.

Performance status [PS] is a measure of general well-being for cancer patients, as assessed by the Multi-Disciplinary Team [MDT], on a scale of 0-4 using the Eastern Co-operative Group performance status scale [ECOG PS] (18) [table 8.4]. A code of 5 signifies that PS is missing.

Table 8.4. Performance status scale

ECOG/ WHO (Zubrod) scale[119]	Short Description	LUCADA Description
0	Asymptomatic	Able to carry out all normal activity without restriction
1	Symptomatic but ambulatory	Restricted in physically strenuous activity but able to walk and do light work
2	In bed < 50% of day	Able to walk and capable of all self care but unable to carry out any work. Up and about more than 50% of waking hours
3	In bed >50& of day	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Bedridden	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	--	Not recorded

8.5 Ethical Approval

Ethical Approval was applied for through the Integrated Research Application System [IRAS] for NHS Research Ethics Committee [REC] approval. The shorter Proportionate Review process was used as only anonymised data was requested. The National Information Governance Board for Health and Social Care [NIGB], which deals with applications to access patient data without consent, were contacted and agreed that, providing mechanisms to prevent small numbers being disclosed and thus potentially-identifying patients were discussed with NYCRIS, NIGB approval was not necessary.

Nor was NHS R&D approval required, although I was initially informed that this would be required from Leeds Teaching Hospitals NHS Trust, as the trust that holds the NYCRIS registry. This did delay the Ethics process whilst this was resolved.

A favourable ethical opinion was obtained from the Proportionate Review sub-committee of the NRES Committee East of England REC on the 13th December 2011 [REC reference 11/EE/0537].

Access to NYCRIS data was applied for using the UK Association of Cancer Registries [UKACR] Information Request form. The UKACR considers the following to be identifiable data items: date of birth, postcode, date or cause of death; therefore I did not request these items but rather anonymised data containing variables derived from these data items.

Data items that could be classified as potentially-identifiable are: individual records even if they do not contain identifiable information and tables of data with low cell counts. However, as I was requesting large datasets for common cancers with all identifiable data anonymised, individual patients should not be identifiable.

8.6 Overview of secondary data analysis analytical methods

The triple linked dataset was used to examine the factors that may influence socio-economic inequalities in lung cancer treatment; referral, diagnosis and treatment time; and survival. The analytical methods are summarised here and detailed statistical methods are given in chapters 9, 10, 11 and 12.

8.6.1 *Socio-economic inequalities in receipt of treatment*

Receipt of treatment by socio-economic position was examined using logistic regression. Other variables that were of interest [age, sex, histology, year of diagnosis, co-morbidity, stage, PS] were examined in unadjusted analyses and included in the adjusted model if significant in the univariable analysis at $p<0.05$ or if thought to be of *a priori* importance. Outcome was receipt of treatment by SEP for:

- Surgery
- Chemotherapy
- Radiotherapy

These results are in chapter 10.

8.6.2 *Socio-economic inequalities in referral, diagnostic and treatment intervals*

Socio-economic inequalities in referral, diagnosis and treatment time for lung cancer patients were examined using Cox proportional hazard models. The following intervals were considered:

- Referral [time from referral to secondary care investigation/first hospital appointment]
- Diagnosis [time from first hospital appointment to diagnosis, and time from GP referral to diagnosis]
- Treatment [time from diagnosis to first treatment, and time from GP referral to first treatment]

Multivariable Cox Proportional Hazard models for each time period were constructed including variables that were thought to be of *a-priori* importance, to examine the hazard ratio [HR] of early referral, diagnosis and treatment, by SEP.

Since 2000, urgent referrals for suspected cancer have been required to have a first hospital appointment [FHA] within 14 days from the date of referral [referral interval]. Since 2005, intervals of 62 days from date of urgent GP referral to first treatment and 31 days from diagnosis to first treatment [treatment intervals] have been in place. The likelihood of referral, diagnosis and treatment within recommended target times by SEP was examined using logistic regression, in multivariable models including other factors [age, sex, histology, year of diagnosis, co-morbidity, stage, PS] that may impact on these time intervals. These results are in chapter 11.

8.6.3 *Socio-economic inequalities in survival*

Survival time was calculated as the interval from the date of diagnosis to the date of death or to the end of follow up at 31/12/2011 for those still alive, when data was censored. All-cause mortality was analysed using Kaplan-Meier plots and Cox proportional hazard models. Kaplan Meier graphs were used to examine univariable influences on all-cause mortality. Cox regression models were used to calculate hazard ratios [HRs] and 95% CIs for all-cause mortality in relation to SEP in multivariable

models. Logistic regression was used to examine the odds of still being alive two years [for 2006 to 2009 and 1999-2005 cohorts] after diagnosis, by SEP.

8.7 Chapter summary

This chapter has given an overview of the secondary data analysis analytical methods and has described the data sources used and variables included, as well as problems with data linkage and missing data. In chapter 9 descriptive results for the dataset are presented. The demographic and clinical characteristics of the patients are examined, as are associations between SEP and a number of variables of interest.

In chapter 10 multivariable analyses to examine socio-economic inequalities in lung cancer treatment are presented. Chapter 11 looks at inequalities in the referral, diagnostic and treatment intervals and chapter 12 examines inequalities in lung cancer survival. Each chapter presents detailed methods, self-contained results and discussion, which places results in context with the literature, discusses the strengths and weaknesses of the study and the potential implications for policy and practice and further research required. Chapter 13 then summarises the overall findings of the thesis, as well as detailing overall methodological strengths and weaknesses of the secondary data analysis, detailing any further implications for policy and practice, and further research required.

Chapter 9. IGIs in lung cancer care – dataset overview and descriptive statistics

9.1 Introduction

In this chapter a descriptive overview of the dataset is given. The demographic and clinical characteristics of the patients in the entire dataset and in the 1999-2005 cohort, 2006-2010 cohort, and 2006-2010 cohort with stage recorded, are examined and compared. Associations between SEP and a number of variables of interest are also examined. Time trends and differences between the datasets are considered and the implications of these differences for the representativeness of the datasets discussed in relation to the proposed multivariable analyses to be carried out.

9.2 Methods

Descriptive statistics for the datasets were calculated using the Chi squared [χ^2] test to describe the characteristics and representativeness of each dataset; to describe characteristics over time; to examine univariable associations between SEP and other patient and tumour characteristics [stage, age, tumour type, PS and CCM score]; and to examine univariable associations between stage, PS and CCM score.

9.3 Results - descriptive statistics

9.3.1 *Characteristics of the datasets*

Table 9.1 shows the demographic and clinical characteristics of patients diagnosed with lung cancer between 1999 and 2010 [n=65,210, excluding those patients who were recorded as DCO] and comparing them with the subset diagnosed from 1999-2005 [n=36,477], 2006-2010 [n=28,733] and, within this, the subset in 2006-2010 with stage recorded [n=7769].

The highest percentage of patients were found in the most deprived quintile [34.8%] with the smallest percentage in the most affluent quintile [11.1%] in the full dataset. A higher percentage of affluent patients were found in the 2006 to 2010 cohort [11.8%] and in the stage subset [12.0%] [table 9.1].

Table 9.1. Demographic and clinical characteristics of patients diagnosed with lung cancer (DCO excluded) between 1999 and 2010, and cohorts diagnosed between 1999-2005, 2006-2010, and 2006-2010 subset with stage recorded

Variable	All patients 1999-2010		cohort 1999-2005		cohort 2006-2010		2006-2010 subset with stage	
	N	%	N	%	N	%	N	%
Deprivation quintile	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
1 (least deprived)	7246	11.1	3,857	10.6	3,389	11.8	931	12.0
2	9265	14.2	5,087	14.0	4,178	14.5	1118	14.4
3	10853	16.6	6,005	16.5	4,848	16.9	1300	16.7
4	15163	23.3	8,453	23.2	6,710	23.4	1831	23.6
5 (most deprived)	22683	34.8	13,075	35.8	9,608	33.4	2589	33.3
Sex	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
Female	28668	44.0	15,414	42.3	13254	46.1	3559	45.8
Male	36542	56.0	21,063	57.7	15479	53.9	4210	54.2
Age group	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
<60	8905	13.7	5,223	14.3	3,682	12.8	1041	13.4
60-69	17130	26.3	9,535	26.1	7,595	26.4	2189	28.2
70-79	24830	38.1	14,582	40.0	10,248	35.7	2843	36.6
80+	14345	22.0	7,137	19.6	7,208	25.1	1696	21.8
Histology	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
NSCLC	34095	52.3	18,972	52.0	15,123	52.6	5116	65.9
SCLC	8599	13.2	5,104	14.0	3,495	12.2	582	7.5
Other	22516	34.5	12,401	34.0	10,115	35.2	2071	26.7
Co-morbidity score	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
0	10063	15.4	6,053	16.6	4,010	14.0	995	12.8
1	4968	7.6	2,588	7.1	2,380	8.3	579	7.5
2	2316	3.6	1,165	3.2	1,151	4.0	278	3.6
3+	1639	2.5	705	1.9	934	3.3	226	2.9
CCM score missing	32,628	50.0	22,453	61.6	10,175	35.4	1,977	25.5
No HES link	13,596	20.9	3,513	9.6	10,083	35.1	3,714	47.8
Stage	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
I	**--**	**--**	**--**	**--**	1,186	4.1	1186	15.3
II	--	--	--	--	552	1.9	552	7.1
III	--	--	--	--	2,273	7.9	2273	29.3
IV	--	--	--	--	3,758	13.1	3758	48.4
Missing/ unknown	**--**	**--**	**--**	**--**	20,964	73.0	**--**	**--**
Performance Status	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
0	**--**	**--**	**--**	**--**	1,842	6.4	1,493	19.2
1-2	--	--	--	--	4,865	16.9	3,870	49.8
3+	--	--	--	--	2,178	7.6	1,763	22.7
Missing/unknown	**--**	**--**	**--**	**--**	19,848	69.1	643	8.3
Surgery	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
Yes	6407	9.8	3,513	9.6	2,894	10.1	1001	12.9
No	58803	90.2	32,964	90.4	25,839	89.9	6768	87.1
Chemotherapy	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
Yes	15996	24.5	7,648	21.0	8,348	29.1	2732	35.2
No	49214	75.5	28,829	79.0	20,385	71.0	5037	64.8
Radiotherapy	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
Yes	22216	34.1	12,602	34.6	9,611	33.5	3069	39.5
No	42994	65.9	23,875	65.5	19,122	66.6	4700	60.5
GP referral date	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
Yes	32,140	49.3	16,688	45.7	15,452	53.8	5,351	68.9
No	33,070	50.7	19,789	54.3	13,281	46.2	2,418	31.1

Table 9.1(cont). Demographic and clinical characteristics of patients diagnosed with lung cancer (DCO excluded) between 1999 and 2010, and cohorts diagnosed between 1999-2005, 2006-2010, and 2006-2010 subset with stage recorded

Variable	All patients 1999-2010		cohort 1999-2005		cohort 2006-2010		2006-2010 subset with stage	
	N	%	N	%	N	%	N	%
Year of Diagnosis	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
1999	5,154	7.9	5,154	14.1	--	--	--	--
2000	5,227	8.0	5,227	14.3	--	--	--	--
2001	5,200	8.0	5,200	14.3	--	--	--	--
2002	5,219	8.0	5,219	14.3	--	--	--	--
2003	5,221	8.0	5,221	14.3	--	--	--	--
2004	5,216	8.0	5,216	14.3	--	--	--	--
2005	5,240	8.0	5,240	14.4	--	--	--	--
2006	5,533	8.5	--	--	5,533	19.3	671	8.6
2007	5,712	8.8	--	--	5,712	19.9	866	11.2
2008	5,851	9.0	--	--	5,851	20.4	1,556	20.0
2009	5,871	9.0	--	--	5,871	20.4	2,140	27.6
2010	5,766	8.8	--	--	5,766	20.1	2,536	32.6
Tumour type	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
Adenocarcinoma	9,463	14.5	5,001	13.7	4,462	15.5	1473	19.0
squamous	13,831	21.2	8,602	23.6	5,229	18.2	1850	23.8
Large-cell	2,140	3.3	1,372	3.8	768	2.7	169	2.2
non-small cell	8,661	13.3	3,997	11.0	4,664	16.2	1624	20.9
Small cell	8,599	13.2	5,104	14.0	3,495	12.2	582	7.5
Other specified	2,511	3.9	1,356	3.7	1,155	4.0	298	3.8
Unspecified carcinoma	4,615	7.1	4,095	11.2	520	1.8	93	1.2
neoplasm	15,390	23.6	6,950	19.1	8,440	29.4	1680	21.6
Alternative histology	**65210**	**100**	**36,477**	**100**	**28733**	**100**	**7769**	**100**
Probable NSCLC	36,606	56.1	20,328	55.7	16,278	56.7	5,414	69.7
SCLC	8,599	13.2	5,104	14.0	3,495	12.2	582	7.5
Unspecified/neoplasm	20,005	30.7	11,045	30.3	8,960	31.2	1,773	22.8

Note: stage and performance status data only available for patients diagnosed between 2006 and 2010

Table 9.1b. Comparison of variable distribution in the datasets

Variables	2006-10 cohort v 1999-2005 cohort		Staged subset v non-staged 2006-10 cohort	
	χ^2	P	χ^2	P
SEP	54.16	<0.001	0.86	0.930
Age	328.21	<0.001	62.65	<0.001
Sex	97.78	<0.001	0.44	0.511
Histology	48.73	<0.001	765.53	<0.001
CCM	244.22	<0.001	39.02	<0.001
Surgery	3.53	0.06	92.99	<0.001
Chemotherapy	567.80	<0.001	192.96	<0.001
Radiotherapy	8.76	0.003	175.30	<0.001

Rates of treatment were higher in the 2006-2010 sub-group that had stage recorded, compared to the 2006-2010 cohort. However, the population distribution by SEP and sex was similar. The age distribution amongst the cohorts was significantly different [table 9.1b]. A higher percentage of patients were diagnosed at an older age in 2006-2010 [25.1% were aged 80+] compared to the earlier years cohort [19.6% were diagnosed at age 80+ in 1999-2005]. However in the cohort with stage recorded higher percentages of younger patients were found [table 9.1].

The sub-population with stage had a much higher percentage of patients diagnosed with NSCLC [65.9% compared to 52.6% in the full 2006-10 cohort]. This is not surprising as staging is not generally carried out for SCLC.

In my systematic review of published research [chapter 7], rates of surgery in UK studies ranged from 4.8% to 13.0% [table 7.5]. Higher rates were found in NSCLC only studies [8.9 to 19.1%]. Chemotherapy rates [any histology] ranged from 15.5 to 23.8% and radiotherapy rates from 20.3 to 63.1%. Any type of treatment rates ranged from 56.3 to 59.6 [table 7.11]. The results from this dataset fall within these ranges for surgery [9.6% in 1999-2005, 10.1% in 2006-2010], chemotherapy [21.0% in 1999-2005, 29.1% in 2006-2010] and radiotherapy [34.6% on 1999-2005 and 33.5% in 2006-2010] [table 9.1].

9.3.2 *Time trends*

Looking at distribution by SEP over time, in 1999 8.5% of patients were in the highest SEP group and 38.7% in the lowest, in 2006 this was 11.2% and 33.5% respectively, and in 2010 this had changed to 12.0% and 32.2% respectively. When looking at the full 1999-2010 dataset these differences were significant [χ^2=225.53, p<0.001] with a higher percentage of people in a higher social class in later years. However, when looking at only the 2006-10 subset there were no significant differences in SEP distribution over this timescale [χ^2 =20.15, p=0.21].

Rates of surgery have increased slightly in recent years but there has been a near doubling of rates of chemotherapy from 1999 [15.2%] to 2010 [29.9%] [table 9.2]. Radiotherapy rates have fallen slightly over time but overall treatment rates have changed little, with rates consistently between 52- 55%.

Table 9.2. Rates of treatment over time

Year	Surgery		Chemotherapy		Radiotherapy		Total
	N	%	N	%	N	%	N
1999	494	9.6	784	15.2	2,059	40.0	5,154
2000	508	9.7	937	17.9	2,013	38.5	5,227
2001	489	9.4	923	17.8	1,881	36.2	5,200
2002	513	9.8	1,048	20.1	1,730	33.2	5,219
2003	505	9.7	1,170	22.4	1,639	31.4	5,221
2004	480	9.2	1,291	24.8	1,615	31.0	5,216
2005	524	10.0	1,495	28.5	1,665	31.8	5,240
2006	505	9.1	1,506	27.2	1,857	33.6	5,533
2007	547	9.6	1,667	29.2	1,865	32.7	5,712
2008	502	8.6	1,681	28.7	1,865	31.9	5,851
2009	682	11.6	1,773	30.2	2,060	35.1	5,871
2010	658	11.4	1,721	29.9	1,964	34.1	5,766
Total	**6,407**	**9.8**	**15,996**	**24.5**	**22,213**	**34.1**	**65,210**

9.3.3 *SEP and patient and tumour characteristics*

Table 9.3 shows the percentage of patients in each SEP group by stage at diagnosis, age at diagnosis, tumour type, PS, and CCM score, as well as the percentage who were recorded as DCO, for the 1999-2005 and 2006-2010 cohorts.

There was a significant association between IMD quintile and being DCO [χ^2 =26.89, p<0.001] in the 1999-2005 cohort, with 1.6% of those in the highest SEP group reported as DCO compared to 3.1% in the lowest. This was not found in the 2006-10 dataset however, where 2.1% of high and low SEP patients were DCO [χ^2 = 6.88, p=0.14] [table 9.3].

IMD quintile was significantly associated with age at diagnosis in both cohorts where those in the most deprived quintile had a younger age at diagnosis [χ^2 = 116.19, p<0.001] in 2006-2010, with 11.4% of those in the most affluent SEP quintile diagnosed at <60 years old compared to 14.2% in the lowest SEP quintile. Similar results were found in 1999-2005 [13.9% compared to 15.3%, χ^2=149.27, p<0.001] [table 9.3].

For the 7769 patients diagnosed in 2006-2010 who had stage recorded, although the percentage who were diagnosed with stage 1 cancer was slightly higher in the highest SEP group compared to the lowest [16.1% compared to 15.0%] and the percentage diagnosed with stage 4 cancer lower [46.6% compared to 49.3%], overall no significant difference in stage at diagnosis was found by SEP [χ^2=4.87, p=0.96] [table 9.3]. Stage was not available for the 1999-2005 cohort.

Table 9.3. Percentage of patients in each SEP quintile (1=least deprived, 5=most deprived), by age at diagnosis, stage at diagnosis, tumour type, CCM score, PS, referral route, and percentage recorded as death-certificate only (DCO)

	SEP quintile: 1999-2005					SEP quintile: 2006-2010				
Variables:	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
DCO										
DCO=yes	1.6	2.5	2.8	2.8	3.1	2.1	2.2	2.0	2.6	2.1
Age at diagnosis										
<60	13.9	13.9	14.2	13.3	15.3	11.4	11.4	11.6	13.4	14.2
60-69	23.8	24.7	24.8	25.9	28.2	25.8	25.4	25.5	25.8	28.0
70-79	39.8	39.5	39.8	40.9	39.7	34.8	36.1	35.5	35.8	35.7
80+	22.6	21.9	21.1	20.0	16.8	28.0	27.3	27.4	25.0	22.0
Stage										
I	**--**	**--**	**--**	**--**	**--**	16.1	15.9	15.1	14.9	15.0
II	--	--	--	--	--	7.2	7.2	7.8	7.2	6.7
III	--	--	--	--	--	30.1	28.2	29.9	29.4	29.0
IV	--	--	--	--	--	46.6	48.8	47.2	48.6	49.3
Tumour type										
Adenocarcinoma	16.3	15.5	14.0	13.5	12.2	19.3	17.2	15.6	14.5	14.2
squamous	19.9	22.6	23.3	23.5	25.2	15.8	17.2	17.6	17.9	20.0
Large-cell	4.7	4.0	3.8	3.7	3.4	2.9	3.1	2.3	2.9	2.4
non-small cell	12.2	11.4	10.4	10.6	10.9	16.8	15.9	16.2	16.9	15.8
Small cell	12.9	13.3	13.2	14.1	14.9	11.8	12.1	12.8	12.3	12.0
Other specified	5.1	4.0	3.8	3.6	3.2	5.0	4.7	3.9	4.0	3.5
Unspecified carcinoma	10.2	10.7	12.0	11.6	11.1	2.1	1.6	1.6	2.0	1.7
neoplasm	18.6	18.5	19.4	19.5	19.0	26.4	28.2	30.0	29.5	30.5
Co-morbidity score										
0	61.9	60.2	59.5	56.2	55.6	54.5	52.3	50.1	44.8	43.3
1-2	32.6	33.5	33.9	36.6	37.6	36.7	37.0	40.4	42.9	45.0
3+	5.6	6.3	6.7	7.2	6.9	8.9	10.7	9.6	12.3	11.6
Perf Status										
0	**--**	**--**	**--**	**--**	**--**	26.3	25.9	20.9	19.0	17.7
1-2	--	--	--	--	--	53.0	52.8	54.2	55.9	55.7
3+	--	--	--	--	--	20.6	21.4	24.9	25.1	26.6
GP referral										
GP ref date = yes	47.2	47.3	46.7	45.7	44.3	53.6	51.5	53.8	54.7	54.2

SEP was associated with histological subtype [tumour]. 16.3% of those in the highest SEP group were diagnosed with adenocarcinoma and 19.9% with squamous cell, whereas in the lowest SEP group 12.2% had adenocarcinoma and 25.2% squamous cell in the 1999-2005 cohort [χ^2=173.74, p<0.001]. Similarly, in the 2006-2010 dataset 19.3% in the highest SEP group were diagnosed with adenocarcinoma and 15.8% squamous cell whereas in the lowest SEP group 14.2% have adenocarcinoma and 20.0% squamous cell [χ^2=145.71, p<0.001] [table 9.3].

There was also an association between tumour type and receipt of surgery. In those diagnosed with an adenocarcinoma 22.7% received surgery, compared to 12.6% with large cell, and 17.6% with squamous cell tumours [table 9.4]. However, the highest rates of surgery were found in the 'other-specified carcinomas' group which encompassed the 3.9% of the dataset that had 54 different tumour types specified.

Table 9.4. Tumour type and receipt of treatment (1999-2010)

	Surgery		Chemotherapy		Radiotherapy		Total
	N	%	N	%	N	%	
Adenocarcinoma	2,148	22.7	2,708	28.6	3,154	33.3	9,463
Squamous	2,437	17.6	3,047	22.0	6,706	48.5	13,831
Large	270	12.6	539	25.2	948	44.3	2,140
Non-small	390	4.5	2,654	30.6	4,175	48.2	8,661
Small	117	1.4	5,783	67.3	3,387	39.4	8,599
Other specified	956	38.1	726	28.9	574	22.9	2,511
Unspecified carcinoma	67	1.5	271	5.9	1,261	27.3	4,615
Neoplasm	22	0.1	268	1.7	2,008	13.1	15,390
Total	6,407	9.8	15,996	24.5	22,213	34.1	65,210

Of the 8885 patients diagnosed in 2006-2010 who had PS recorded, 26.6% in the lowest SEP group had poor performance status [PS 3-4] compared to 20.6% in the highest SEP group, whereas 26.3% in the highest SEP group had good PS [PS=0] compared to 17.7% in the lowest group [table 9.3]. These differences were statistically significant [χ^2= 69.02, p<0.001].

Of the 8475 patients who had a CCM score recorded in 2006-2010, 11.6% in the lowest SEP group had three or more co-morbidities recorded compared to 8.9% in the highest SEP group, whereas 54.4% in the highest SEP group had 0 co-morbidities recorded compared to 43.3% in the lowest SEP group [table 9.3]. These differences were statistically significant (χ^2=63.44, p<0.001). Similar results were seen for the 10,511 patients who had a CCM score recorded in 1999-2005 [χ^2=23.73, p=0.003].

SEP was significantly associated with having a GP referral date [χ^2=20.62, p<0.001 for 1999-2005 cohort and χ^2=11.998, p=0.02 for 2006-2010 cohort] although contrasting patterns of results were seen in the two cohorts. In 1999-2005 those in the lowest SEP group had lower rates of GP referral date recorded compared to those in the highest but for 2006-2010, in contrast to what might have been expected, those in the lowest SEP group had a higher rate of GP referral date recorded than those in the highest SEP group.

9.3.4 *Stage, PS and co-morbidity*

In the 2006-2010 dataset 7126 patients had stage and PS recorded. A significant association between stage and PS was found [χ^2 = 436.95, p<0.001] with high levels of good PS in those with early stage cancer compared to late stage lung cancer [table 9.5].

Only 2078 patients had both stage and co-morbidity score recorded. A slightly higher rate of recorded co-morbidity was found in those who had early stage cancer [of those with stage 1 cancer 56.8% had co-morbidity compared with 49.4% for those with stage 4 cancer] but no significant association between stage and co-morbidity was found [χ^2 = 10.17, p=0.12] [table 9.5].

Table 9.5. Percentage rates of PS and co-morbidity by stage

%	PS (n=7126)			Co-morbidity Score (n=2078)		
Stage	**0**	**1-2**	**3-4**	**0**	**1-2**	**3+**
1	35.9	51.0	13.1	43.2	43.7	13.1
2	29.0	54.5	16.5	41.8	48.4	9.8
3	22.7	59.0	18.3	48.3	40.7	11.0
4	14.1	52.4	33.5	50.5	39.4	10.0

Both co-morbidity and PS can be used as surrogate measures of suitability for lung cancer treatment. The number of co-morbidities was significantly associated with PS score, where those with good PS had lower rates of high co-morbidity [χ^2 =78.53, p<0.001]. Only 2434 patients had both a PS and CCM score recorded and 63.0% of those who had a PS score of 0 [good health] also had no co-morbidities, 31.5% had 1-2 co-morbidities and 5.5% had 3+ co-morbidities. However, 36.3% of those with a PS score of 3-4 [poor health] also had no co-morbidities recorded [table 9.6].

Table 9.6. Percentage rates for number of co-morbidities by performance status score

%	Co-morbidity Score		
Performance Status	**0**	**1-2**	**3+**
0 (good PS)	63.0	31.5	5.5
1-2	48.6	41.1	10.4
3-4 (poor PS)	36.3	48.6	15.2

9.4 Discussion

As these are descriptive results only, a general discussion is presented here. Implications for policy and practice and further research will be discussed in the next four chapters when the multivariable results are presented.

When the demographic and clinical characteristics of the patients in the different cohorts were compared, differences were found. The 2006-2010 cohort was significantly different from the 1999-2005 cohort on all variables examined except for sex. Rates of treatment were significantly higher in the 2006-2010 sub-group that had stage recorded and it had a higher percentage of younger patients and NSCLC patients, compared to the full 2006-2010 cohort. The population distribution by SEP and sex was not significantly different however. The staged cohort does therefore appear to be younger and more likely to undergo treatment.

Over a third of the northern lung cancer population were in the most deprived SEP quintile. National deprivation quintiles are used by cancer registries so that, across England, the definition of most and least deprived is consistent (244). Quintiles are based on population so that each quintile has an equal number of residents. This does mean that, in areas with deprivation higher than the national average [such as NYCRIS] there may be low numbers of people within the population in the least deprived quintiles. This could be considered a limitation when using regional data. Unfortunately the population data for each quintile was not available, to examine any skew in population distribution in regional compared to national data. However as there were data for over 65,000 patients available, the numbers in all quintiles were large.

In order to determine patient delay [time between onset of symptoms and initial presentation to GP], data should ideally be obtained from patients or from GP records.

Patient records were not available for this study and as a date is not recorded in the Registry dataset for the onset of symptoms it was not possible to look at patient delay by SEP unless a proxy measure such as stage of disease at presentation or mode of presentation [elective/emergency] was employed. Death within one year of diagnosis can be used as a proxy measure of patient delay for some cancers but would not be suitable for lung cancer which has short expected survival.

Mode of presentation was requested but was not available from NYCRIS [due to problems with its calculation] but stage at diagnosis was available, as was the number of patients recorded as DCO. It has previously been suggested that DCO registrations are more common in deprived communities (143) but a study using NYCRIS data did not find this, using breast and colorectal cancer data (247). In this study a socio-economic gradient in DCO cases by SEP was found in the 1999-2005 cohort, with DCO rates nearly double in the most deprived quintile compared to the least deprived. However this was not found in the 2006-2010 cohort.

Socio-economic inequalities in stage at diagnosis have been noted for some cancers which might suggest that there are differences in timeliness of patient presentation by SEP (66), where stage is used as a marker of late presentation and thus as a proxy measure of patient delay. However, previous studies examining socio-economic inequalities in stage at diagnosis for lung cancer did not find any significant differences by SEP (66, 68) suggesting that timeliness of patient presentation to the GP with lung cancer does not differ by SEP. We also found no evidence of socio-economic inequalities in stage at diagnosis. Results using DCO as a proxy measure of patient delay suggest that there were inequalities in time to patient presentation in the early years but unfortunately stage at diagnosis was not available for the 1999-2005 cohort to confirm this. However, using both stage at diagnosis and DCO, no evidence for inequalities in delay in patient presentation by SEP was found for the 2006-2010 cohort, although these were univariable analyses.

A non-significantly higher rate of co-morbidity was found in those who had early stage compared to late stage cancer. Other studies have found that patients with severe co-morbidity were likely to have early-stage lung cancer (157), suggesting that those who suffer from a number of different medical conditions may have greater contact with

health professionals and so are more likely to have their cancer detected at an earlier stage.

A significant association between stage and PS was found but none was found between stage and CCM score. Although co-morbidity and PS measure different things [number of concurrent health conditions and general health status respectively], both can be used as surrogate measures of suitability for lung cancer treatment. Those with good PS were less likely to have severe co-morbidity [65.7% of those who had a PS score of 0 had 0 co-morbidities]. However 41.9% of those with a PS score of 3-4 [poor health] also had 0 co-morbidities recorded. There is therefore an association between the two measures but, as can be seen here, a large percentage of those who have poor health do not have any co-morbidities recorded.

Descriptive statistics for the univariable associations between SEP and receipt of treatment, time to referral, diagnosis and treatment, and survival are described in chapters 10-12.

9.5 Chapter summary

Associations between SEP and a number of variables of interest were examined. SEP was univariably associated with age at diagnosis, tumour type, PS, CCM score and GP referral, but not with stage at diagnosis. An association between tumour type and receipt of treatment was also found.

The demographic and clinical characteristics of the patients in the entire dataset and in the 1999-2005 cohort, 2006-2010 cohort, and 2006-2010 cohort with stage recorded, were examined and compared. Significant differences were found between cohorts. The implications of these differences on the representativeness of the cohorts and any subsequent differences in outcome observed between cohorts will be considered in more detail in the following chapters.

Chapter 10 now goes on to examine socio-economic inequalities in lung cancer treatment.

Chapter 10. Socio-economic inequalities in receipt of lung cancer treatment

Summary

Background

Socio-economic inequalities in receipt of lung cancer treatment have been demonstrated in my systematic review and meta-analysis, in both universal [UHCS] and non-universal healthcare systems. These findings could not be explained by type of healthcare system or stage at diagnosis. However, not all of the included studies reported details of stage and histology, both of which influence treatment type, and very few UHCS studies took co-morbidity or performance status into account. The review recommended that the reasons for socio-economic inequalities in treatment should be more thoroughly investigated.

Cancer registry [NYCRIS], Hospital Episode Statistics [HES] and lung cancer audit [LUCADA] data-sets from the North of England were linked in order to examine the influence of stage, histology, performance status and co-morbidity on socio-economic inequalities in lung cancer treatment.

Methods

Multivariable logistic regression was used to examine the likelihood of receipt of surgery, chemotherapy and radiotherapy by socio-economic position [SEP] in patients diagnosed between 1999-2005 [n=36,477] of whom 32,974 had a linked HES record, and in patients diagnosed between 2006-2010 [n=28,733], and in a subset of whom had stage [n=7769] and PS recorded in LUCADA.

Results (for 2006-2010 cohort)

Socio-economic inequalities in receipt of surgery and chemotherapy, but not radiotherapy, were found after control for age, sex, histology, PS and co-morbidity. The odds of receiving surgery were significantly lower in the lowest compared to the highest SEP group in the full cohort [OR=0.75, CI 0.65 to 0.86, $p<0.001$]. Inequalities in receipt of surgery were substantially attenuated by adjustment for tumour type [OR=0.83, CI 0.71 to 0.96, $p=0.01$].

Patients in the lowest SEP group were significantly less likely to receive chemotherapy in the full cohort [OR= 0.60, CI 0.54 to 0.67, p<0.001], but not in the stage-subset when PS was included in the model [OR= 0.84, CI 0.68 to 1.02, p=0.08].

Conclusions

Socio-economic inequalities in performance status statistically explain socio-economic inequalities in receipt of chemotherapy in the selective subset of patients whose cancer was staged but not in the full cohort.

Socio-economic inequalities in receipt of surgery cannot be statistically explained by inequalities in stage, PS or co-morbidity. However, socio-economic inequalities in tumour type account for some of the inequalities in surgery by SEP. Patients in lower SEP groups are more likely to be diagnosed with squamous cell cancer [a tumour type strongly associated with smoking] and are less likely to receive surgery than patients in higher SEP groups, who are more likely to be diagnosed with adenocarcinoma.

10.1 Introduction

Socio-economic inequalities in receipt of lung cancer treatment were demonstrated in my systematic review and meta-analysis (236), in both universal [UHCS] and non-universal healthcare systems [chapter 6]. These findings could not be explained by the type of healthcare system or by socio-economic inequalities in stage at diagnosis. However, not all of the included UK studies reported details of stage and histology, both of which influence treatment type (236), and very few UHCS studies took co-morbidity into account. Performance status [PS], a measure of patient well-being, is also a factor that has not been previously well explored. The systematic review recommended that the reasons for socio-economic inequalities in treatment should be more thoroughly investigated in better quality UHCS studies, including statistical control for co-morbidity, stage and histology (236).

Although co-morbidity and PS measure different things [the number of concurrent health conditions and general health status respectively] both variables may be used as surrogate measures of suitability for lung cancer treatment when patients are assessed. It is unclear how well co-morbidity and PS capture this 'fitness for treatment' concept but, as the number of co-morbidities and PS vary by SEP, this may help explain why inequalities are found. I also wanted to explore whether differences in rates of histological subtype by SEP might be important as, in the descriptive analyses [chapter 9], SEP was associated with tumour type, and different rates of treatment were also found by tumour type.

Cancer registry, Hospital Episode Statistics [HES] and lung cancer audit [LUCADA] data-sets were linked in order to examine the role that socio-economic inequalities in stage, histological subtype, PS and co-morbidity might play in contributing to socio-economic inequalities in lung cancer treatment in the North-East of England.

10.2 Methods

10.2.1 *Data*

For details of data sources and variables see chapter 8, sections 8.2 and 8.4.

10.2.2 *Regression analyses*

Multivariable logistic regression was used to examine the likelihood of receipt of surgery, chemotherapy and radiotherapy by SEP, in the 1999-2005 and 2006-2010 cohorts. The analyses were conducted as follows: in the 1999-2005 dataset controlling for age, sex, histology [or histological subtype], co-morbidity, year of diagnosis and GP referral; in the 2006-2010 dataset and, within this, on the subgroup that had stage recorded [n=7769], controlling for age, sex, histology [or histological subtype], year of diagnosis, GP referral, PS and stage, and including and excluding co-morbidity. Interaction between SEP and histology was also explored. The R^2 statistic was examined to determine the amount of variance in receipt of treatment explained by each model. Odds ratios [ORs] with 95% confidence intervals [CIs] for the likelihood of receipt of treatment in the lower SEP groups compared to the highest SEP group were reported. A likelihood ratio test was performed to determine the overall significance of each categorical variable.

Cancer type [histology] was classified as confirmed non-small cell lung cancer [NSCLC], SCLC and other histology as previously described. Sub group analyses including only morphologically-specified lung cancers were also carried out. The 'unspecified carcinoma/neoplasm' subtypes were excluded and the 'other specified carcinoma' subtype was included as probable NSCLC. Receipt of surgery was examined for probable NSCLC-only patients. Receipt of chemotherapy and radiotherapy were examined separately in probable NSCLC and SCLC populations.

10.3 Results

Table 9.1 shows the demographic and clinical characteristics of the lung cancer patients included in the study.

10.3.1 *Surgery*

Socio-economic inequalities in receipt of surgery were found. When age, sex, histology or tumour type, year of diagnosis, co-morbidity, performance status, stage and GP referral were taken into account, socio-economic inequalities in receipt of treatment remained.

10.3.1.1 *1999-2005*

The rate of surgery in the highest SEP group was 11.7% compared to 8.5% in the lowest SEP group, with a univariable OR for receipt of surgery of 0.70, 95% CI 0.62 to 0.78, p<0.001 in the lowest compared to the highest.

The odds of surgery were significantly lower in the lowest compared to the highest SEP group [OR=0.64, 95% CI 0.57 to 0.73, p<0.001] in a multivariable analysis including age, sex, histology, co-morbidity and GP referral [table 10.1]. When histology was further broken down into tumour type then the SEP OR was attenuated [OR=0.70, 95% CI 0.61 to 0.79, p<0.001] and the treatment variance explained by the model greatly improved [from R^2=13.33 to 22.91] [table 10.1].

10.3.1.2 *2006-2010*

The rate of surgery in the highest SEP group was 11.8% compared to 9.5% in the lowest SEP group, with a univariable OR for receipt of surgery of 0.78 [95% CI 0.69 to 0.89, p<0.001] in the lowest compared to the highest.

The odds of surgery were significantly lower in the lowest compared to the highest SEP group in the multivariable analysis when stage and PS [but not CCM] were included [OR=0.75, 95% CI 0.65 to 0.86, p<0.001] [table 10.2]. The addition of co-morbidity to the model made no substantial change to this OR. Significant interaction between SEP and histology was found. Similarly to the 1999-2005 cohort, when histology was further broken down into tumour type then the SEP OR was attenuated [OR=0.83, 95% CI 0.71 to 0.96, p=0.0013] and the treatment variance explained by the model greatly improved [from R^2=24.04 to 35.17].

Older patients were significantly less likely to receive surgery [OR=0.14, 95% CI 0.12 to 0.17, p<0.001], for those aged 80+, and [OR =0.65, 95% CI 0.57 to 0.73, p<0.001 for those aged 70-79], compared to the youngest group [aged <60] in a multivariable model, but when histology was further broken down into tumour type then the OR was attenuated [to OR=0.22, 95% CI 0.18 to 0.27, p<0.001, and OR=0.79, 95% CI 0.70 to 0.91, p=0.001, respectively] [table 10.2]. 56% of those aged 80+ had their tumour type recorded as a neoplasm compared to 8% in the youngest age group. Those with late stage cancer and those with poor performance status were also significantly less

likely to receive surgery. However, even when taking all these factors into account, age and socio-economic inequalities in receipt of surgery were still found.

10.3.1.2.1 *2006-2010: subgroup with stage*

In the subgroup that had stage recorded [n=7769], although overall 12.9% of these patients received surgery, 51.2% of stage I patients received surgery, with 35.3% in stage II, so that receipt of surgery was highly dependent on stage. The odds of receiving treatment in the lowest SEP group compared to the highest were significantly lower in the univariable [OR=0.67, 95% CI 0.54 to 0.82, p=0.001] and adjusted analysis [OR=0.60, 95% CI 0.45 to 0.81, p=0.001] [table 10.3].

10.3.1.2.2 *2006-2010: probable NSCLC only*

When looking at receipt of surgery for those with probable NSCLC only [n=16,278] socio-economic inequalities in receipt of treatment were found in the multivariable analysis [OR=0.84, 95% CI 0.72 to 0.98, p=0.025], in the lowest compared to the highest SEP group [table 10.4].

Table 10.1. OR of receipt of lung cancer surgery, by selected patient, tumour and system factors for those diagnosed between 1999 and 2005 (DCO cases excluded)

Variable	Receipt of Surgery		Adjusted – selected[1] (n=36,477, R^2=13.33)				Adjusted – selected[2] (n=36,477, R^2=22.91)			
	N	%	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile	**3,513**	**9.6**				**<0.001**				**<0.001**
1 (least deprived)	452	11.7	1.00				1.00			
2	565	11.1	0.92	0.80	1.06	0.25	0.95	0.83	1.10	0.53
3	592	9.9	0.81	0.71	0.93	0.002	0.85	0.73	0.97	0.02
4	794	9.4	0.77	0.67	0.87	<0.001	0.81	0.71	0.93	<0.001
5 (most deprived)	1,110	8.5	0.64	0.57	0.73	<0.001	0.70	0.61	0.79	<0.001
Sex	**3,513**	**9.6**				**0.009**				**0.05**
Female	1,459	9.5	1.00				1.00			
Male	2,054	9.8	0.91	0.84	0.98	0.009	0.92	0.85	1.00	0.05
Age group	**3,513**	**9.6**				**<0.001**				**<0.001**
<60	852	16.3	1.00				1.00			
60-69	1,296	13.6	0.82	0.75	0.91	<0.001	0.91	0.82	1.00	0.06
70-79	1,248	8.6	0.50	0.45	0.55	<0.001	0.60	0.54	0.66	<0.001
80+	117	1.6	0.10	0.08	0.13	<0.001	0.15	0.12	0.18	<0.001
Histology	**3,513**	**9.6**				**<0.001**				
NSCLC	2,897	15.3	1.00							
SCLC	63	1.2	0.06	0.05	0.08	<0.001				
Other	553	4.5	0.38	0.35	0.42	<0.001				
Co-morbidity score	**3,513**	**9.6**				**<0.001**				**<0.001**
0	740	12.2	1.00				1.00			
1-2	318	8.5	0.75	0.65	0.86	<0.001	0.82	0.70	0.95	0.01
3+	58	8.2	0.79	0.59	1.05	0.11	0.92	0.68	1.24	0.57
CCM missing	2,351	10.5	0.73	0.67	0.80	<0.001	0.78	0.71	0.86	<0.001
No HES link	46	1.3	0.13	0.10	0.18	<0.001	0.18	0.13	0.24	<0.001
Year of Diagnosis	**3,513**	**9.6**				**0.46**				**0.07**
1999	494	9.6	1.00				1.00			
2000	508	9.7	1.04	0.90	1.19	0.61	1.07	0.93	1.23	0.33
2001	489	9.4	0.95	0.83	1.09	0.45	1.10	0.95	1.26	0.21
2002	513	9.8	0.96	0.84	1.10	0.57	1.14	0.99	1.32	0.06
2003	505	9.7	0.95	0.83	1.09	0.46	1.16	1.01	1.34	0.04
2004	480	9.2	0.89	0.77	1.02	0.09	1.06	0.92	1.23	0.39
2005	524	10.0	0.97	0.84	1.11	0.63	1.25	1.08	1.43	0.002
GP referral	**3,513**	**9.6**				**<0.001**				**<0.001**
No	1,560	7.9	1.00				1.00			
Yes	1,953	11.7	1.29	1.20	1.39	<0.001	1.20	1.11	1.30	<0.001
Histological sub-type	**3,513**	**9.6**								**<0.001**
Adenocarcinoma	1,150	23.0					1.00			
squamous	1,426	16.6					0.73	0.66	0.80	<0.001
Large-cell	146	10.6					0.41	0.34	0.49	<0.001
non-small cell	175	4.4					0.15	0.13	0.18	<0.001
Other specified	486	35.8					1.81	1.59	2.07	<0.001
Small cell	63	1.2					0.04	0.03	0.05	<0.001
Unspecified carcinoma	53	1.3					0.06	0.05	0.08	<0.001
Neoplasm	14	0.2					0.01	0.01	0.02	<0.001

[1] Mutually adjusted for SEP, sex, age, histology, co-morbidity score, year of diagnosis and GP referral

[2] Mutually adjusted for SEP, sex, age, co-morbidity score, year of diagnosis, GP referral and histological subtype

Table 10.2. OR of receipt of lung cancer surgery, by selected patient, tumour and system factors (DCO cases excluded) for 2006-2010 cohort

Variable	Receipt of surgery (2894/28733)		Adjusted – selected[1] (n=28,733, R^2=24.04)				Adjusted – selected[2] (n=28,733, R^2=35.17)			
	N	%	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile	**2,894**	**10.1**				**<0.001**				**0.01**
1 (least deprived)	400	11.8	1.00				1.00			
2	458	11.0	0.92	0.78	1.08	0.32	0.92	0.77	1.09	0.33
3	512	10.6	0.91	0.78	1.07	0.26	0.97	0.82	1.15	0.75
4	613	9.1	0.75	0.65	0.87	<0.001	0.81	0.69	0.95	0.009
5 (most deprived)	911	9.5	0.75	0.65	0.86	<0.001	0.83	0.71	0.96	0.013
Sex	**2,894**	**10.1**				**<0.001**				**<0.001**
Female	1,405	10.6	1.00				1.00			
Male	1,489	9.6	0.80	0.73	0.87	<0.001	0.78	0.71	0.86	<0.001
Age group	**2,894**	**10.1**				**<0.001**				**<0.001**
<60	560	15.2	1.00				1.00			
60-69	1,118	14.7	0.96	0.85	1.08	0.50	1.05	0.92	1.19	0.47
70-79	1,048	10.2	0.65	0.57	0.73	<0.001	0.79	0.70	0.91	0.001
80+	168	2.3	0.14	0.12	0.17	<0.001	0.22	0.18	0.27	<0.001
Histology	**2,894**	**10.1**				**<0.001**				
NSCLC	2,348	15.5	1.00							
SCLC	54	1.6	0.08	0.06	0.11	<0.001				
Other	492	4.9	0.43	0.38	0.48	<0.001				
Year of Diagnosis	**2,894**	**10.1**				**<0.001**				**<0.001**
2006	505	9.1	1.00				1.00			
2007	547	9.6	1.04	0.91	1.19	0.58	1.10	0.95	1.27	0.19
2008	502	8.6	0.95	0.82	1.09	0.47	0.96	0.82	1.11	0.58
2009	682	11.6	1.33	1.16	1.52	<0.001	1.33	1.15	1.53	<0.001
2010	658	11.4	1.38	1.20	1.59	<0.001	1.25	1.08	1.45	0.003
Stage	**2,894**	**10.1**				**<0.001**				**<0.001**
I	607	51.2	1.00				1.00			
II	195	35.3	0.41	0.32	0.53	<0.001	0.43	0.33	0.56	<0.001
III	144	6.3	0.04	0.03	0.05	<0.001	0.04	0.03	0.06	<0.001
IV	55	1.5	0.01	0.01	0.02	<0.001	0.01	0.01	0.02	<0.001
Missing	1,893	9.0	0.12	0.10	0.14	<0.001	0.11	0.09	0.14	<0.001
Performance Status	**2,894**	**10.1**				**<0.001**				**<0.001**
0	583	31.7	1.00				1.00			
1-2	480	9.9	0.30	0.25	0.36	<0.001	0.33	0.28	0.40	<0.001
3-4	15	0.7	0.03	0.02	0.05	<0.001	0.05	0.03	0.09	<0.001
Missing/ unknown	1,816	9.2	0.34	0.28	0.41	<0.001	0.41	0.34	0.51	<0.001
GP referral	**2,894**	**10.1**				**<0.001**				**<0.001**
No	979	7.4	1.00				1.00			
Yes	1,915	12.4	1.37	1.25	1.50	<0.001	1.26	1.14	1.39	<0.001
Histological subtype	**2,894**	**10.1**								**<0.001**
Adenocarcinoma	998	22.4					1.00			
squamous	1,011	19.3					0.86	0.77	0.97	0.01
Large cell	124	16.2					0.64	0.51	0.80	<0.001
Non-small	215	4.6					0.19	0.16	0.22	<0.001
Other specified	470	40.7					2.40	2.06	2.80	<0.001
Small	54	1.6					0.06	0.04	0.07	<0.001
Unspecified carcinoma	14	2.7					0.14	0.08	0.24	<0.001
Neoplasm	8	0.1					0.01	0.00	0.01	<0.001

[1] Mutually adjusted for SEP, sex, age, histology, year of diagnosis, stage, PS and GP referral

[2] Mutually adjusted for SEP, sex, age, year of diagnosis, stage, PS, GP referral and histological subtype

Table 10.3. OR of receipt of lung cancer surgery, by selected patient, tumour and system factors (DCO cases excluded) for 2006-2010 cohort with stage recorded

Variable	Receiving surgery (1001/7769)		Adjusted – selected[1] (n=7769, R^2=46.99)				Adjusted – selected[2] (n=7676, R^2=53.61)			
	N	%	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile	**1,001**	**12.9**				**0.0007**				**0.003**
1 (least deprived)	156	16.8	1.00				1.00			
2	162	14.5	0.79	0.56	1.10	0.16	0.72	0.51	1.04	0.08
3	177	13.6	0.76	0.55	1.05	0.09	0.77	0.54	1.08	0.13
4	199	10.9	0.54	0.40	0.74	<0.001	0.53	0.38	0.75	<0.001
5 (most deprived)	307	11.9	0.60	0.45	0.81	0.001	0.61	0.44	0.83	0.002
Sex	**1,001**	**12.9**				**0.02**				**0.12**
Female	485	13.6	1.00				1.00			
Male	516	12.3	0.81	0.67	0.97	0.02	0.85	0.70	1.04	0.12
Age group	**1,001**	**12.9**				**<0.001**				**<0.001**
<60	179	17.2	1.00				1.00			
60-69	398	18.2	1.00	0.76	1.32	0.99	1.13	0.85	1.51	0.41
70-79	353	12.4	0.56	0.43	0.75	<0.001	0.66	0.49	0.90	0.007
80+	71	4.2	0.15	0.11	0.22	<0.001	0.19	0.13	0.28	<0.001
Histology	**1,001**	**12.9**				**<0.001**				
NSCLC	852	16.7	1.00							
SCLC	18	3.1	0.25	0.14	0.43	<0.001				
Other	131	6.3	0.48	0.37	0.62	<0.001				
Year of Diagnosis	**1,001**	**12.9**				**<0.001**				**0.0001**
2006	84	12.5	1.00				1.00			
2007	116	13.4	1.14	0.77	1.69	0.52	1.09	0.71	1.66	0.70
2008	162	10.4	1.22	0.84	1.78	0.29	1.11	0.75	1.66	0.60
2009	311	14.5	1.97	1.39	2.78	<0.001	1.81	1.25	2.62	0.002
2010	328	12.9	2.13	1.51	3.01	<0.001	1.74	1.20	2.52	0.003
Stage	**1,001**	**12.9**				**<0.001**				**<0.001**
I	607	51.2	1.00				1.00			
II	195	35.3	0.42	0.32	0.53	<0.001	0.43	0.33	0.56	<0.001
III	144	6.3	0.04	0.03	0.05	<0.001	0.04	0.03	0.05	<0.001
IV	55	1.5	0.01	0.01	0.01	<0.001	0.01	0.01	0.01	<0.001
Performance Status	**1,001**	**12.9**				**<0.001**				**<0.001**
0	498	33.4	1.00				1.00			
1-2	413	10.7	0.31	0.26	0.38	<0.001	0.36	0.29	0.45	<0.001
3-4	12	0.7	0.03	0.02	0.06	<0.001	0.06	0.03	0.11	<0.001
Missing/ unknown	78	12.1	0.33	0.23	0.46	<0.001	0.36	0.25	0.52	<0.001
GP referral	**1,001**	**12.9**				**0.29**				**0.85**
No	243	10.1	1.00				1.00			
Yes	758	14.2	1.12	0.91	1.39	0.29	1.02	0.81	1.28	0.85
Histological subtype	**1,001**	**12.9**								**<0.001**
Adenocarcinoma	372	25.3					1.00			
squamous	372	20.1					0.67	0.52	0.85	0.001
Large cell	32	18.9					0.55	0.31	0.98	0.04
Non-small	76	4.7					0.19	0.13	0.26	<0.001
Other specified	130	43.6					2.12	1.44	3.12	<0.001
Small	18	3.1					0.15	0.09	0.27	<0.001
Unspecified carcinoma	0	0.0					--			
Neoplasm	1	0.1					0.003	0.00	0.02	<0.001

[1] Mutually adjusted for SEP, sex, age, histology, year of diagnosis, stage, PS and GP referral

[2] Mutually adjusted for SEP, sex, age, year of diagnosis, stage, PS, GP referral and histological subtype

Table 10.4. OR of receipt of lung cancer surgery, by selected patient, tumour and system factors (DCO cases excluded) for 2006-2010 cohort with probable NSCLC

Variable	Probable NSCLC	Receiving surgery		Unadjusted				Adjusted – selected[1] (n=16,278, R^2=23.74)			
	N	N	%	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile	**16,278**	**2,818**	**17.3**				**0.001**				**0.02**
1 (least deprived)	2,024	389	19.2	1.00				1.00			
2	2,430	451	18.6	0.96	0.82	1.11	0.58	0.93	0.78	1.11	0.43
3	2,696	494	18.3	0.94	0.81	1.09	0.44	0.96	0.81	1.14	0.68
4	3,768	592	15.7	0.78	0.68	0.90	0.001	0.80	0.68	0.95	0.009
5 (most deprived)	5,360	892	16.6	0.84	0.74	0.96	0.009	0.84	0.72	0.98	0.03
Sex	**16,278**	**2,818**	**17.3**				**<0.001**				**<0.001**
Female	7060	1359	19.3	1.00				1.00			
Male	9218	1459	15.8	0.79	0.73	0.86	<0.001	0.79	0.72	0.87	<0.001
Age group	**16,278**	**2,818**	**17.3**				**<0.001**				**<0.001**
<60	2679	544	20.3	1.00				1.00			
60-69	5126	1085	21.2	1.05	0.94	1.18	0.37	1.05	0.92	1.20	0.50
70-79	5293	1025	17.3	0.82	0.73	0.92	0.001	0.80	0.70	0.92	0.001
80+	2550	164	6.4	0.27	0.22	0.32	<0.001	0.22	0.18	0.27	<0.001
Year of Diagnosis	**16,278**	**2,818**	**17.3**				**<0.001**				**<0.001**
2006	3141	489	15.6	1.00				1.00			
2007	3269	530	16.2	1.05	0.92	1.20	0.48	1.10	0.95	1.27	0.21
2008	3285	493	15.0	0.96	0.84	1.10	0.53	0.97	0.83	1.13	0.71
2009	3358	668	19.9	1.35	1.18	1.53	<0.001	1.34	1.16	1.55	<0.001
2010	3225	638	19.8	1.34	1.17	1.52	<0.001	1.24	1.07	1.44	0.005
Stage	**16,278**	**2,818**	**17.3**				**<0.001**				**<0.001**
I	917	595	64.9	1.00				1.00			
II	437	192	43.9	0.42	0.34	0.54	<0.001	0.44	0.33	0.58	<0.001
III	1701	141	8.3	0.05	0.04	0.06	<0.001	0.05	0.04	0.06	<0.001
IV	2359	54	2.3	0.01	0.01	0.02	<0.001	0.01	0.01	0.02	<0.001
Missing	10,864	1836	16.9	0.11	0.10	0.13	<0.001	0.12	0.10	0.16	<0.001
Performance Status	**16,278**	**2,818**	**17.3**				**<0.001**				**<0.001**
0	1528	574	37.6	1.00				1.00			
1-2	3467	470	13.6	0.26	0.23	0.30	<0.001	0.33	0.28	0.40	<0.001
3-4	835	13	1.6	0.03	0.02	0.05	<0.001	0.04	0.02	0.08	<0.001
Missing/ unknown	10,448	1761	16.9	0.34	0.30	0.38	<0.001	0.39	0.32	0.48	<0.001
GP referral	**16,278**	**2,818**	**17.3**				**<0.001**				**<0.001**
No	6304	946	15.0	1.00				1.00			
Yes	9974	1872	18.8	1.31	1.20	1.43	<0.001	1.26	1.15	1.40	<0.001
Histological sub-type	**16,278**	**2,818**	**17.3**				**<0.001**				**<0.001**
Adenocarcinoma	4462	998	22.4	1.00				1.00			
squamous	5229	1011	19.3	0.83	0.75	0.92	<0.001	0.86	0.77	0.96	0.009
Large cell	768	124	16.2	0.67	0.54	0.82	<0.001	0.64	0.51	0.80	<0.001
Non-small	4664	215	4.6	0.17	0.14	0.20	<0.001	0.19	0.16	0.22	<0.001
Other specified	1155	470	40.7	2.38	2.08	2.73	<0.001	2.39	2.05	2.79	<0.001

[1]Mutually adjusted for SEP, sex, age, year of diagnosis, stage, PS, GP referral and histological subtype

10.3.2 *Chemotherapy*

10.3.2.1 *1999-2005*

In the adjusted model SEP was strongly associated with receipt of chemotherapy. Those in the lowest SEP group were significantly less likely to receive chemotherapy [OR=0.60, 95% CI 0.54 to 0.67, p<0.001] [table 10.5]. Older patients were significantly less likely to receive chemotherapy, as were those with co-morbidities. Rates of chemotherapy increased over time with 15.2% receiving chemotherapy in 1999, increasing to 28.5% in 2005.

Table 10.5. OR of receipt of lung cancer chemotherapy, by selected patient, tumour and system factors (DCO cases excluded) for those diagnosed between 1999 and 2005

Variable	Receiving chemotherapy		Unadjusted				Adjusted – selected[1] (n=36,477, R^2=32.84)			
	N	%	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile	**7,648**	**21.0**				**<0.001**				**<0.001**
1 (least deprived)	961	24.9	1.00				1.00			
2	1,108	21.8	0.84	0.76	0.93	0.001	0.75	0.67	0.85	<0.001
3	1,196	19.9	0.75	0.68	0.83	<0.001	0.67	0.59	0.76	<0.001
4	1,720	20.4	0.77	0.70	0.84	<0.001	0.69	0.61	0.77	<0.001
5 (most deprived)	2,663	20.4	0.77	0.71	0.84	<0.001	0.60	0.54	0.67	<0.001
Sex	**7,648**	**21.0**				**0.001**				**0.39**
Female	3,356	21.8	1.00				1.00			
Male	4,292	20.4	0.92	0.87	0.97	0.001	0.97	0.91	1.04	0.39
Age group	**7,648**	**21.0**				**<0.001**				**<0.001**
<60	2393	45.8	1.00				1.00			
60-69	2,945	30.9	0.53	0.49	0.57	<0.001	0.48	0.44	0.52	<0.001
70-79	2,074	14.2	0.20	0.18	0.21	<0.001	0.18	0.17	0.20	<0.001
80+	236	3.3	0.04	0.04	0.05	<0.001	0.04	0.04	0.05	<0.001
Histology	**7,648**	**21.0**				**<0.001**				**<0.001**
NSCLC	3,582	18.9	1.00				1.00			
SCLC	3,402	66.7	8.59	8.02	9.20	<0.001	12.87	11.86	13.96	<0.001
Other	664	5.4	0.24	0.22	0.26	<0.001	0.41	0.37	0.45	<0.001
Co-morbidity score	**7,648**	**21.0**				**<0.001**				**<0.001**
0	1,302	21.5	1.00				1.00			
1-2	556	14.8	0.63	0.57	0.71	<0.001	0.75	0.66	0.85	<0.001
3-4	68	9.7	0.39	0.30	0.50	<0.001	0.47	0.35	0.63	<0.001
CCM missing	5,643	25.1	1.22	1.14	1.31	<0.001	1.06	0.97	1.15	0.21
No HES link	79	2.3	0.08	0.07	0.11	<0.001	0.14	0.11	0.18	<0.001
Year of Diagnosis	**7,648**	**21.0**				**<0.001**				**<0.001**
1999	784	15.2	1.00				1.00			
2000	937	17.9	1.22	1.10	1.35	0.00	1.35	1.19	1.53	<0.001
2001	923	17.8	1.20	1.08	1.33	0.00	1.46	1.28	1.66	<0.001
2002	1,048	20.1	1.40	1.26	1.55	0.00	1.70	1.50	1.93	<0.001
2003	1,170	22.4	1.61	1.46	1.78	0.00	2.20	1.95	2.49	<0.001
2004	1,291	24.8	1.83	1.66	2.02	0.00	2.64	2.34	2.99	<0.001
2005	1,495	28.5	2.23	2.02	2.45	0.00	3.56	3.16	4.02	<0.001
GP referral	**7,648**	**21.0**				**<0.001**				**<0.001**
No	3,265	16.5	1.00				1.00			
Yes	4,383	26.3	1.80	1.71	1.90	<0.001	1.86	1.74	1.98	<0.001

[1]Mutually adjusted for SEP, sex, age, histology, co-morbidity score, year of diagnosis and GP referral

10.3.2.2 *2006-2010*

SEP was associated with receipt of treatment in the 2006-2010 subset when age, sex, histology, year of diagnosis, GP referral, stage and PS were included in the model [OR=0.60, 95% CI 0.54 to 0.67, p<0.001] [table 10.6].

Table 10.6. OR of receipt of lung cancer chemotherapy, by selected patient, tumour and system factors (DCO cases excluded) for 2006-2010 cohort

Variable	Receiving chemotherapy (8348/28733)		Unadjusted				Adjusted – selected[1] (n=28,733, R^2=33.01)			
	N	%	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile	**8,348**	**29.1**				**<0.001**				**<0.001**
1 (least deprived)	1,133	33.4	1.00				1.00			
2	1,275	30.5	0.87	0.79	0.96	0.007	0.83	0.74	0.94	<0.001
3	1,425	29.4	0.83	0.75	0.91	<0.001	0.78	0.69	0.88	<0.001
4	1,898	28.3	0.79	0.72	0.86	<0.001	0.67	0.60	0.75	<0.001
5 (most deprived)	2,617	27.2	0.75	0.69	0.81	<0.001	0.60	0.54	0.67	<0.001
Sex	**8,348**	**29.1**				**0.29**				**0.96**
Female	3,810	28.8	1.00				1.00			
Male	4,538	29.3	1.03	0.98	1.08	0.29	1.00	0.94	1.07	0.96
Age group	**8,348**	**29.1**				**<0.001**				**<0.001**
<60	2,221	60.3	1.00				1.00			
60-69	3,332	43.9	0.51	0.47	0.56	<0.001	0.51	0.46	0.55	<0.001
70-79	2,452	23.9	0.21	0.19	0.22	<0.001	0.22	0.20	0.24	<0.001
80+	343	4.8	0.03	0.03	0.04	<0.001	0.04	0.04	0.05	<0.001
Histology	**8,348**	**29.1**				**<0.001**				**<0.001**
NSCLC	5,366	35.5	1.00				1.00			
SCLC	2,381	68.1	3.89	3.59	4.20	<0.001	5.63	5.12	6.18	<0.001
Other	601	5.9	0.11	0.11	0.13	<0.001	0.22	0.20	0.25	<0.001
Year of Diagnosis	**8,348**	**29.1**				**0.005**				**0.03**
2006	1,506	27.2	1.00				1.00			
2007	1,667	29.2	1.10	1.02	1.20	0.02	1.17	1.06	1.30	<0.001
2008	1,681	28.7	1.08	0.99	1.17	0.07	1.06	0.96	1.17	0.27
2009	1,773	30.2	1.16	1.07	1.25	<0.001	1.11	1.00	1.23	0.05
2010	1,721	29.9	1.14	1.05	1.23	<0.001	1.11	1.00	1.23	0.05
Stage	**8,348**	**29.1**				**<0.001**				**<0.001**
I	223	18.8	1.00				1.00			
II	163	29.5	1.81	1.43	2.29	<0.001	2.11	1.60	2.78	<0.001
III	1,032	45.4	3.59	3.04	4.25	<0.001	5.45	4.46	6.67	<0.001
IV	1,314	35.0	2.32	1.98	2.73	<0.001	4.30	3.54	5.23	<0.001
Missing	5,616	26.8	1.58	1.36	1.83	<0.001	3.46	2.83	4.24	<0.001
Performance Status	**8,348**	**29.1**				**<0.001**				**<0.001**
0	1,151	62.5	1.00				1.00			
1-2	2,067	42.5	0.44	0.40	0.50	<0.001	0.46	0.40	0.53	<0.001
3-4	113	5.2	0.03	0.03	0.04	<0.001	0.04	0.03	0.05	<0.001
Missing/ unknown	5,017	25.3	0.20	0.18	0.22	<0.001	0.29	0.25	0.34	<0.001
GP referral date	**8,348**	**29.1**				**<0.001**				**<0.001**
No	2,566	19.3	1.00				1.00			
Yes	5,782	37.4	2.50	2.37	2.64	<0.001	2.17	2.03	2.32	<0.001

[1]Mutually adjusted for SEP, sex, age, histology, year of diagnosis, stage, PS and GP referral

10.3.2.2.1 *2006-2010: subset with stage recorded*

In the subset of patients who had stage recorded, in a multivariable analysis including age and sex, a significant association was seen [OR=0.72, 95% CI 0.61 to 0.86, P<0.001], and this was also observed with the stepwise addition of other variables; histology, year of diagnosis, and stage, with a similar OR in the lowest compared to the highest SEP group, in all cases [table 10.7]. However, on the addition of performance status to the model the OR was attenuated and this association was no longer observed [OR=0.84, 95% CI 0.68 to 1.02, p=0.08] [table 10.7]. Including performance status also greatly increased the treatment variance explained by the model [R^2=25.84 without PS, 34.58 with]. An identical pattern was also seen in the probable NSCLC-only subset with stage recorded [results not shown]. Socio-economic differences in performance status appear to account for the observed socio-economic differences in receipt of chemotherapy in this staged subgroup.

10.3.2.2.2 *2006-2010: probable NSCLC and SCLC separately*

When chemotherapy was examined separately in probable NSCLC and SCLC populations, socio-economic inequalities in receipt of chemotherapy were found for NSCLC [OR=0.66, 95% CI 0.58 to 0.74, p<0.001] [table 10.8] and SCLC [OR=0.57, 95% CI 0.42 to 0.75, p<0.001] [table 10.9]. For probable NSCLC likelihood of chemotherapy increased over time but this was not seen for SCLC.

Table 10.7. OR of receipt of lung cancer chemotherapy, by selected patient, tumour and system factors (DCO cases excluded) for 2006-2010 cohort with stage recorded

Variable	Receiving chemotherapy (2732/7769)		Adjusted – selected[1] (n=7769, R^2=25.84)				Adjusted – selected[2] (n=7769, R^2=34.58)			
	N	%	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile	**2,732**	**35.2**				**<0.001**				**0.16**
1 (least deprived)	351	37.7	1.00				1.00			
2	414	37.0	0.97	0.78	1.20	0.76	0.99	0.79	1.24	0.91
3	445	34.2	0.85	0.69	1.05	0.14	1.01	0.81	1.26	0.94
4	638	34.8	0.78	0.64	0.94	0.01	0.90	0.73	1.11	0.32
5 (most deprived)	884	34.1	0.68	0.56	0.82	<0.001	0.84	0.68	1.02	0.08
Sex	**2,732**	**35.2**				**0.79**				**0.80**
Female	1,255	35.3	1.00				1.00			
Male	1,477	35.1	0.98	0.88	1.10	0.79	0.98	0.87	1.11	0.80
Age group	**2,732**	**35.2**				**<0.001**				**<0.001**
<60	690	66.3	1.00				1.00			
60-69	1,103	50.4	0.48	0.40	0.56	<0.001	0.54	0.45	0.65	<0.001
70-79	821	28.9	0.19	0.16	0.23	<0.001	0.25	0.21	0.30	<0.001
80+	118	7.0	0.04	0.03	0.05	<0.001	0.06	0.04	0.07	<0.001
Histology	**2,732**	**35.2**				**<0.001**				**<0.001**
NSCLC	2,140	41.8	1.00				1.00			
SCLC	411	70.6	4.03	3.25	4.99	<0.001	6.21	4.85	7.95	<0.001
Other	181	8.7	0.20	0.17	0.24	<0.001	0.29	0.24	0.35	<0.001
Year of Diagnosis	**2,732**	**35.2**				**0.21**				**0.07**
2006	211	31.5	1.00				1.00			
2007	323	37.3	1.36	1.06	1.74	0.02	1.44	1.11	1.88	0.01
2008	556	35.7	1.22	0.97	1.53	0.08	1.37	1.08	1.74	0.01
2009	758	35.4	1.21	0.97	1.51	0.08	1.29	1.02	1.62	0.03
2010	884	34.9	1.20	0.97	1.49	0.09	1.30	1.04	1.64	0.02
GP referral	**2,732**	**35.2**				**<0.001**				**<0.001**
No	603	24.9	1.00				1.00			
Yes	2,129	39.8	2.15	1.90	2.45	<0.001	2.01	1.75	2.30	<0.001
Stage	**2,732**	**35.2**				**<0.001**				**<0.001**
I	223	18.8	1.00				1.00			
II	163	29.5	1.83	1.41	2.39	<0.001	2.16	1.64	2.84	<0.001
III	1,032	45.4	3.94	3.26	4.77	<0.001	5.58	4.55	6.84	<0.001
IV	1,314	35.0	2.41	2.01	2.89	<0.001	4.43	3.64	5.40	<0.001
Performance Status	**2,732**	**35.2**								**<0.001**
0	933	62.5					1.00			
1-2	1,561	40.3					0.39	0.34	0.46	<0.001
3-4	78	4.4					0.03	0.02	0.04	<0.001
Missing	160	24.9					0.25	0.19	0.31	<0.001

[1]Mutually adjusted for SEP, sex, age, histology, year of diagnosis, GP referral and stage

[2]Mutually adjusted for SEP, sex, age, histology, year of diagnosis, GP referral, stage and PS

Table 10.8. OR of receipt of lung cancer chemotherapy, by selected patient, tumour and system factors for those diagnosed between 2006 and 2010 (DCO cases excluded) for probable NSCLC

Variable	Unadjusted (n=16,278)				Adjusted – selected[1] (n=16,278, R^2=18.26)			
	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile				**<0.001**				**<0.001**
1 (least deprived)	1.00				1.00			
2	0.90	0.80	1.02	0.10	0.88	0.77	1.01	0.08
3	0.84	0.74	0.94	0.004	0.84	0.74	0.97	0.014
4	0.80	0.71	0.89	<0.001	0.73	0.64	0.83	<0.001
5 (most deprived)	0.76	0.68	0.84	<0.001	0.66	0.58	0.74	<0.001
Sex				**<0.001**				**0.97**
Female	1.00				1.00			
Male	0.96	0.90	1.02	0.18	1.00	0.93	1.07	0.97
Age group				**<0.001**				**<0.001**
<60	1.00				1.00			
60-69	0.55	0.50	0.61	<0.001	0.54	0.49	0.60	<0.001
70-79	0.24	0.22	0.27	<0.001	0.23	0.21	0.25	<0.001
80+	0.05	0.04	0.06	<0.001	0.05	0.04	0.05	<0.001
Year of Diagnosis				**<0.001**				**0.007**
2006	1.00				1.00			
2007	1.23	1.10	1.36	<0.001	1.24	1.11	1.39	<0.001
2008	1.23	1.11	1.36	<0.001	1.14	1.01	1.28	0.03
2009	1.28	1.15	1.42	<0.001	1.13	1.00	1.27	0.04
2010	1.35	1.22	1.50	<0.001	1.17	1.04	1.32	0.01
Stage				**<0.001**				**<0.001**
I	1.00				1.00			
II	1.87	1.46	2.41	<0.001	2.22	1.67	2.94	<0.001
III	3.71	3.09	4.46	<0.001	6.02	4.88	7.43	<0.001
IV	2.80	2.35	3.34	<0.001	5.03	4.10	6.16	<0.001
missing	1.70	1.45	2.00	<0.001	3.30	2.66	4.10	<0.001
Performance Status				**<0.001**				**<0.001**
0	1.00				1.00			
1-2	0.47	0.42	0.53	<0.001	0.48	0.42	0.56	<0.001
3-4	0.04	0.03	0.05	<0.001	0.03	0.02	0.05	<0.001
Missing/ unknown	0.31	0.28	0.34	<0.001	0.38	0.32	0.45	<0.001
GP referral				**<0.001**				**<0.001**
No	1.00				1.00			
Yes	2.08	1.94	2.23	<0.001	2.08	1.93	2.25	<0.001

[1]Mutually adjusted for SEP, sex, age, year of diagnosis, stage, PS and GP referral

Table 10.9. OR of receipt of lung cancer chemotherapy, by selected patient, tumour and system factors for those diagnosed between 2006 and 2010 (DCO cases excluded) for SCLC

Variable	Unadjusted (n=3495)				Adjusted – selected[1] (n=3495, R^2=15.83)			
	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile				**0.06**				**0.0006**
1 (least deprived)	1.00				1.00			
2	0.73	0.54	0.97	0.03	0.74	0.53	1.02	0.07
3	0.77	0.58	1.03	0.07	0.70	0.51	0.95	0.02
4	0.70	0.54	0.91	0.009	0.58	0.43	0.78	<0.001
5 (most deprived)	0.70	0.54	0.90	0.006	0.57	0.42	0.75	<0.001
Sex				**0.87**				**0.56**
Female	1.00				1.00			
Male	1.01	0.88	1.17	0.87	0.95	0.81	1.12	0.56
Age group				**<0.001**				**<0.001**
<60	1.00				1.00			
60-69	0.58	0.45	0.75	<0.001	0.55	0.42	0.71	<0.001
70-79	0.32	0.25	0.41	<0.001	0.31	0.24	0.40	<0.001
80+	0.10	0.07	0.13	<0.001	0.09	0.06	0.12	<0.001
Year of Diagnosis				**0.39**				**0.13**
2006					1.00			
2007	1.02	0.81	1.28	0.86	1.01	0.79	1.30	0.91
2008	0.91	0.73	1.14	0.42	0.81	0.63	1.03	0.09
2009	1.12	0.89	1.40	0.34	1.00	0.77	1.29	0.98
2010	0.92	0.74	1.15	0.47	0.79	0.61	1.03	0.08
Performance Status				**<0.001**				**<0.001**
0	1.00				1.00			
1-2	0.40	0.24	0.66	<0.001	0.50	0.30	0.84	0.01
3-4	0.04	0.02	0.07	<0.001	0.05	0.03	0.10	<0.001
Missing/ unknown	0.18	0.11	0.29	<0.001	0.22	0.13	0.36	<0.001
GP referral				**<0.001**				**<0.001**
No	1.00				1.00			
Yes	2.16	1.87	2.49	<0.001	2.24	1.91	2.64	<0.001

[1]Mutually adjusted for SEP, sex, age, year of diagnosis, PS and GP referral

10.3.3 *Radiotherapy*

10.3.3.1 *1999-2005*

In the 1999 to 2005 data no association between SEP and receipt of radiotherapy was found in the unadjusted analysis or in the adjusted model [table 10.10] when co-morbidity was included [OR= 0.98, 95% CI 0.91 to 1.06, p=0.67].

10.3.3.2 *2006-2010*

No association between SEP and receipt of radiotherapy was found in the 2006-2010 cohort [adjusted OR= 1.03, CI 0.94 to 1.13, p=0.48] [table 10.11]. Similarly, in the analysis of receipt of radiotherapy in the subset of patients who had stage recorded [n=7769], SEP was not associated with radiotherapy [OR=1.01, 95% CI 0.86 to 1.19, p=0.88] in the adjusted model including age, sex, year of diagnosis, histology, GP referral status, stage and PS [results not shown]. The addition of co-morbidity to the model did not change this. The rate of receipt of radiotherapy was higher [39.5%] in the staged subset compared to in the full cohort [33.5%].

10.3.3.2.1 *2006-2010: probable NSCLC and SCLC separately*

When radiotherapy was examined separately in probable NSCLC [n=16,278] and SCLC [n=3495] populations, socio-economic inequalities in receipt of radiotherapy were found for probable NSCLC [OR=1.18, 95% CI 1.06 to 1.31, p=0.003] [table 10.12] but not SCLC [OR=0.84, 95% CI 0.66 to 1.07, p=0.16] when comparing OR in the lowest SEP group to the highest [table 10.13].

Table 10.10. OR of receipt of lung cancer radiotherapy, by selected patient, tumour and system factors (DCO cases excluded) for those diagnosed between 1999 and 2005

Variable	Receiving radiotherapy (12,602/36,477)		Unadjusted (n=36,477)				Adjusted – selected[1] (n=36,477, R^2=7.23)			
	N	%	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile	**12,602**	**34.6**				**0.65**				**0.65**
1 (least deprived)	1,312	34.0	1.00				1.00			
2	1,781	35.0	1.04	0.96	1.14	0.33	1.02	0.93	1.12	0.63
3	2,092	34.8	1.04	0.95	1.13	0.40	1.03	0.94	1.12	0.55
4	2,875	34.0	1.00	0.92	1.08	1.00	0.99	0.91	1.07	0.76
5 (most deprived)	4,542	34.7	1.03	0.96	1.11	0.41	0.98	0.91	1.06	0.67
Sex	**12,602**	**34.6**				**<0.001**				**0.16**
Female	5,092	33.0	1.00				1.00			
Male	7,510	35.7	1.12	1.08	1.17	<0.001	1.03	0.99	1.08	0.16
Age group	**12,602**	**34.6**				**<0.001**				**<0.001**
<60	2,354	45.1	1.00				1.00			
60-69	3,815	40.0	0.81	0.76	0.87	<0.001	0.83	0.78	0.90	<0.001
70-79	4,938	33.9	0.62	0.59	0.67	<0.001	0.71	0.66	0.76	<0.001
80+	1,495	21.0	0.32	0.30	0.35	<0.001	0.46	0.43	0.50	<0.001
Histology	**12,602**	**34.6**				**<0.001**				**<0.001**
NSCLC	8,371	44.1	1.00				1.00			
SCLC	1,825	35.8	0.70	0.66	0.75	<0.001	0.68	0.63	0.72	<0.001
Other	2,406	19.4	0.30	0.29	0.32	<0.001	0.38	0.36	0.40	<0.001
Co-morbidity score	**12,602**	**34.6**				**<0.001**				**<0.001**
0	2,123	35.1	1.00				1.00			
1-2	1,200	32.0	0.87	0.80	0.95	0.002	1.01	0.92	1.10	0.87
3+	175	24.8	0.61	0.51	0.73	<0.001	0.77	0.64	0.92	0.005
CCM missing	8,410	37.5	1.11	1.04	1.18	0.001	1.02	0.96	1.09	0.52
No HES link	694	19.8	0.46	0.41	0.50	<0.001	0.62	0.56	0.69	<0.001
Year of Diagnosis	**12,602**	**34.6**				**<0.001**				**<0.001**
1999	2,059	40.0	1.00				1.00			
2000	2,013	38.5	0.94	0.87	1.02	0.13	0.96	0.89	1.05	0.40
2001	1,881	36.2	0.85	0.79	0.92	<0.001	0.83	0.77	0.91	<0.001
2002	1,730	33.2	0.75	0.69	0.81	<0.001	0.70	0.65	0.76	<0.001
2003	1,639	31.4	0.69	0.63	0.75	<0.001	0.66	0.60	0.72	<0.001
2004	1,615	31.0	0.67	0.62	0.73	<0.001	0.65	0.59	0.70	<0.001
2005	1,665	31.8	0.70	0.65	0.76	<0.001	0.67	0.61	0.73	<0.001
GP referral	**12,602**	**34.6**				**<0.001**				**<0.001**
No	5,581	28.2	1.00				1.00			
Yes	7,021	42.1	1.85	1.77	1.93	<0.001	1.63	1.55	1.70	<0.001

[1]Mutually adjusted for SEP, sex, age, histology, co-morbidity score, year of diagnosis and GP referral

Table 10.11. OR of receipt of lung cancer radiotherapy, by selected patient, tumour and system factors (DCO cases excluded) for 2006-2010 cohort

Variable	Receiving radiotherapy (9611/28,733)		Unadjusted (n=28,733)				Adjusted – selected[1] (n=28,733, R^2=11.20)			
	N	%	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile	**9,611**	**33.5**				**0.80**				**0.80**
1 (least deprived)	1,126	33.2	1.00				1.00			
2	1,401	33.5	1.01	0.92	1.12	0.78	1.04	0.94	1.16	0.41
3	1,612	33.3	1.00	0.91	1.10	0.98	1.03	0.93	1.14	0.60
4	2,215	33.0	0.99	0.91	1.08	0.83	1.00	0.91	1.10	0.96
5 (most deprived)	3,257	33.9	1.03	0.95	1.12	0.48	1.03	0.94	1.13	0.48
Sex	**9,611**	**33.5**				**<0.001**				**0.06**
Female	4,258	32.1	1.00				1.00			
Male	5,353	34.6	1.12	1.06	1.17	<0.001	1.05	1.00	1.11	0.06
Age group	**9,611**	**33.5**				**<0.001**				**<0.001**
<60	1,707	46.4	1.00				1.00			
60-69	3,140	41.3	0.82	0.75	0.88	<0.001	0.86	0.79	0.93	<0.001
70-79	3,330	32.5	0.56	0.52	0.60	<0.001	0.67	0.62	0.73	<0.001
80+	1,434	19.9	0.29	0.26	0.31	<0.001	0.49	0.45	0.54	<0.001
Histology	**9,611**	**33.5**				**<0.001**				**<0.001**
NSCLC	6,612	43.7	1.00				1.00			
SCLC	1,562	44.7	1.04	0.97	1.12	0.30	1.06	0.98	1.14	0.15
Other	1,437	14.2	0.21	0.20	0.23	<0.001	0.30	0.28	0.32	<0.001
Year of Diagnosis	**9,611**	**33.5**				**0.003**				**0.009**
2006	1,857	33.6	1.00				1.00			
2007	1,865	32.7	0.96	0.89	1.04	0.30	0.95	0.88	1.03	0.25
2008	1,865	31.9	0.93	0.86	1.00	0.06	0.87	0.80	0.94	0.001
2009	2,060	35.1	1.07	0.99	1.16	0.09	0.99	0.91	1.08	0.78
2010	1,964	34.1	1.02	0.95	1.11	0.58	0.95	0.87	1.04	0.28
Stage	**9,611**	**33.5**				**<0.001**				**<0.001**
I	370	31.2	1.00				1.00			
II	234	42.4	1.62	1.32	2.00	0.00	1.56	1.25	1.94	<0.001
III	1,206	53.1	2.49	2.15	2.89	0.00	2.42	2.07	2.83	<0.001
IV	1,259	33.5	1.11	0.97	1.28	0.14	1.22	1.05	1.42	<0.011
Missing	6,542	31.2	1.00	0.88	1.14	1.00	1.51	1.29	1.76	<0.001
Performance Status	**9,611**	**33.5**				**<0.001**				**<0.001**
0	832	45.2	1.00				1.00			
1-2	2,375	48.8	1.16	1.04	1.29	0.01	1.43	1.27	1.60	<0.001
3-4	387	17.8	0.26	0.23	0.30	<0.001	0.52	0.44	0.61	<0.001
Missing/ unknown	6,017	30.3	0.53	0.48	0.58	<0.001	0.89	0.78	1.01	0.07
GP referral	**9,611**	**33.5**				**<0.001**				**<0.001**
No	3,262	24.6	1.00				1.00			
Yes	6,349	41.1	2.14	2.04	2.25	<0.001	1.70	1.61	1.79	<0.001

[1]Mutually adjusted for SEP, sex, age, histology, year of diagnosis, stage, PS and GP referral

Table 10.12. OR of receipt of lung cancer radiotherapy, by selected patient, tumour and system factors for those diagnosed between 2006 and 2010 (DCO cases excluded) for probable NSCLC

Variable	Unadjusted (n=16,278)				Adjusted – selected[1] (n=16,278, R^2=2.98)			
	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile				**0.005**				**0.04**
1 (least deprived)	1.00				1.00			
2	1.07	0.95	1.21	0.24	1.08	0.96	1.22	0.21
3	1.08	0.96	1.21	0.20	1.08	0.96	1.22	0.20
4	1.12	1.01	1.25	0.04	1.11	0.99	1.24	0.08
5 (most deprived)	1.20	1.08	1.33	0.001	1.18	1.06	1.31	0.003
Sex				**0.08**				**0.09**
Female	1.00				1.00			
Male	1.06	0.99	1.13	0.08	1.06	0.99	1.13	0.09
Age group				**<0.001**				**<0.001**
<60	1.00				1.00			
60-69	0.94	0.86	1.03	0.21	0.92	0.84	1.02	0.11
70-79	0.78	0.71	0.86	<0.001	0.77	0.70	0.85	<0.001
80+	0.69	0.62	0.77	<0.001	0.70	0.63	0.79	<0.001
Year of Diagnosis				**0.56**				**0.03**
2006	1.00				1.00			
2007	1.00	0.91	1.10	1.00	0.98	0.89	1.09	0.74
2008	0.95	0.86	1.05	0.36	0.87	0.79	0.97	0.01
2009	1.04	0.94	1.15	0.43	0.94	0.84	1.04	0.20
2010	1.00	0.91	1.11	0.97	0.88	0.79	0.98	0.02
Stage				**<0.001**				**<0.001**
I	1.00				1.00			
II	1.90	1.50	2.40	<0.001	1.86	1.47	2.36	<0.001
III	3.09	2.61	3.66	<0.001	3.04	2.55	3.61	<0.001
IV	1.54	1.31	1.81	<0.001	1.58	1.34	1.86	<0.001
Missing	1.46	1.27	1.69	<0.001	1.77	1.48	2.12	<0.001
Performance Status				**<0.001**				**<0.001**
0	1.00				1.00			
1-2	1.47	1.30	1.66	<0.001	1.53	1.34	1.73	<0.001
3-4	0.60	0.50	0.71	<0.001	0.66	0.54	0.79	<0.001
Missing/ unknown	0.92	0.82	1.02	0.13	1.03	0.89	1.20	0.71
GP referral				**<0.001**				**<0.001**
No	1.00				1.00			
Yes	1.63	1.53	1.74	<0.001	1.58	1.48	1.69	<0.001

[1]Mutually adjusted for SEP, sex, age, histology, year of diagnosis, stage, PS and GP referral

Table 10.13. OR of receipt of lung cancer radiotherapy, by selected patient, tumour and system factors for those diagnosed between 2006 and 2010 (DCO cases excluded) for SCLC

Variable	Unadjusted (n=3495)				Adjusted – selected[1] (n=3495, R^2=6.63)			
	OR	(95% CI)		P	OR	(95% CI)		P
Deprivation quintile				**0.48**				**0.35**
1 (least deprived)	1.00				1.00			
2	0.84	0.64	1.09	0.19	0.86	0.65	1.13	0.28
3	1.01	0.78	1.29	0.96	0.98	0.75	1.27	0.85
4	0.88	0.69	1.12	0.31	0.82	0.64	1.06	0.13
5 (most deprived)	0.90	0.72	1.13	0.38	0.84	0.66	1.07	0.16
Sex				**0.06**				**0.04**
Female	1.00				1.00			
Male	0.88	0.77	1.00	0.06	0.86	0.75	0.99	0.04
Age group				**<0.001**				**<0.001**
<60	1.00				1.00			
60-69	0.69	0.57	0.84	<0.001	0.67	0.55	0.82	<0.001
70-79	0.46	0.38	0.56	<0.001	0.47	0.39	0.58	<0.001
80+	0.31	0.24	0.41	<0.001	0.32	0.25	0.42	<0.001
Year of Diagnosis				**<0.001**				**0.008**
2006	1.00				1.00			
2007	1.03	0.83	1.28	0.77	1.02	0.82	1.28	0.84
2008	1.14	0.93	1.41	0.22	1.07	0.86	1.34	0.53
2009	1.53	1.24	1.89	<0.001	1.45	1.16	1.82	0.001
2010	1.48	1.19	1.83	<0.001	1.41	1.12	1.77	0.003
Performance Status				**<0.001**				**<0.001**
0	1.00				1.00			
1-2	0.47	0.34	0.65	<0.001	0.53	0.38	0.75	<0.001
3-4	0.11	0.07	0.17	<0.001	0.14	0.09	0.22	<0.001
Missing/ unknown	0.31	0.23	0.42	<0.001	0.41	0.30	0.56	<0.001
GP referral				**<0.001**				**<0.001**
No	1.00				1.00			
Yes	1.89	1.64	2.16	<0.001	1.78	1.54	2.05	<0.001

[1]Mutually adjusted for SEP, sex, age, year of diagnosis, PS and GP referral

10.4 Discussion

10.4.1 *Principal findings*

Socio-economic inequalities in receipt of surgery and chemotherapy but not radiotherapy for lung cancer were found in the full cohort analyses [1999-2005 and 2006-2010]. However, socio-economic inequalities in receipt of chemotherapy were not found in the subset with stage recorded when PS was included in the model.

Socio-economic inequalities in receipt of lung cancer treatment were demonstrated in my systematic review and meta-analysis, in both universal [UHCS] and non-universal healthcare systems (236). However, the quality of the included studies varied and not all of the UK studies reported details of stage and histology, both of which influence the type of treatment that is likely to be offered. Factors such as co-morbidity and performance status [PS], that might help to explain socio-economic inequalities in receipt of treatment, had not been previously well explored. We were able to take all these factors into account and still socio-economic inequalities in receipt of surgery remained.

Socio-economic inequalities in performance status appear to account for much of the socio-economic inequalities in receipt of chemotherapy in the staged subset. Socio-economic differences in tumour type may partially account for some of the socio-economic differences in receipt of surgery observed.

10.4.2 *Strengths and limitations*

To our knowledge this is one of the first studies to use multiple dataset linkage [NYCRIS, HES and LUCADA] in order to examine the factors that may influence socio-economic inequalities in lung cancer treatment in a large dataset. Only one other recent 2012 study has used these three datasets but did not include PS or tumour type in the analysis (157). In the 1999-2005 cohort I was able to take into account co-morbidity and in the 2006-2010 analyses I was also able to take into account stage and performance status. Therefore I have been able to include a range of potential confounders that previous studies have not, and inequalities in receipt of surgery remained. The high levels of missing stage, PS and co-morbidity data are, however, a limitation.

It appeared that those patients referred via the GP were more likely to receive treatment. Having a GP referral date recorded was used to determine mode of presentation [via the GP or directly to secondary care], as a proxy measure of urgency. However, it is possible that some patients may have been referred via their GP, but this has not been recorded within the registry dataset.

When histology was further broken down into histological [tumour] subtypes the OR of likelihood of receipt of treatment in the most compared to the least deprived SEP group was attenuated. The highest rates of surgery were found in the 'other-specified carcinomas' group, of which over a quarter were highly-operable carcinoid tumours, and the remaining 73% consisted of 52 different tumour-type codes. It may be that poor histological classification of non-standard tumour types [by putting these into the 'other' rather than NSCLC histology category] may account for this attenuation, as patients in the higher SEP groups had higher rates of these non-standardly coded tumour types than did the lowest SEP groups.

10.4.3 *Interpretation of results and comparison with other studies*

10.4.3.1 *Receipt of surgery*

Socio-economic inequalities in receipt of surgery may be partially explained by socio-economic differences in tumour type as, when histology was further broken down into histological subtypes, the OR of likelihood of receipt of treatment in the most compared to the least deprived SEP group was attenuated. It appears that higher levels of more operable tumour types are found in the least deprived SEP group.

A previous study using Thames Cancer Registry data found that adenocarcinoma is less clearly associated with deprivation compared to other histological subtypes, as its development is less strongly linked to smoking (248). This current study also found a higher proportion of adenocarcinoma and lower proportion of the squamous subtype in higher SEP patients compared to the lowest SEP group, with a significant association between SEP group and histological subtype.

In the 2006-2010 cohort, in the highest SEP group 19.3% of patients had adenocarcinoma compared to 14.2% in the lowest; and 15.8% had squamous subtypes compared to 20.0% in the lowest. As 22.7% of patients with adenocarcinoma received

surgery but only 17.6% with squamous cell carcinoma did it does appear that some types of tumours are more operable than others and that socio-inequalities in receipt of surgery may be partly explained by socio-economic differences in tumour type. However, although no other UK studies could be identified that examined surgery by tumour type, a study using Danish cancer registry data for patients diagnosed between 2005-2010 (249) found similar rates of surgery in patients with adenocarcinoma [24%] but found higher rates of surgery in squamous cell patients [23%] than I did, with squamous rate similar to their adenocarcinoma rate. They therefore concluded that tumour type did not greatly influence the likelihood of receiving surgery in that population (249).

Some further smoking-related confounding could however be occurring as, although I was unable to determine smoking status from this study, smokers have generally poorer health (71) and it may be this, rather than specifically tumour type, that determines receipt of surgery. However, I was able to include PS in the analysis, which is a measure of general well-being, as well as co-morbidity score. Smokers have also been shown to be less likely to receive treatment even after adjustment for co-morbidity (250) although the reasons for this are not clear.

Around 30% of tumour type was recorded as morphologically unspecified [unspecified carcinoma and neoplasm] although this is a similar level to that recorded in other UK registries (20). Only 0.1% of those diagnosed with a neoplasm received surgery. Interestingly, 56% of those aged 80+ had their tumour type recorded as a neoplasm compared to 8% in the youngest age group and so this is likely to explain much of why those in the older age group did not receive surgery. Neoplasm is a general term for an unclassified tumour and is used for those patients who have undergone clinical investigation only. This could suggest that older patients do not receive surgery because their cancer has not been as thoroughly investigated and classified as those in younger patients. It is unclear whether older patients do not receive such thorough investigation because they are less well, have poorer PS and so are less able to tolerate this, or whether there is genuine bias occurring here, where older patients receive less thorough investigation than younger patients due to more nihilistic attitudes from clinicians.

Previous studies have shown age-related inequalities in histological diagnosis and treatment even after co-morbidity and PS were taken into account, which would suggest age-discrimination (251). A Scottish study found that the selection of investigations initially carried out varied by geographical location and according to individual clinician practice rather than being guided by the therapeutic intention. Patients who were referred for surgery tended to be younger and had good PS (252). Although the study was carried out prior to treatment guidelines being introduced it is possible that similar practices still occur. A study in the Netherlands that examined lung cancer treatment found that less than half the patients were treated according to guidelines and the proportion decreased with age (72). Age inequalities in treatment remained in the multivariable analyses here when PS and co-morbidity were taken into account which would suggest that older-patients who are fit enough for treatment are not receiving it.

10.4.3.3 *Receipt of radiotherapy*

Socio-economic inequalities in receipt of radiotherapy were not found apart from in the analysis of NSCLC-only patients, where more deprived NSCLC patients were significantly more likely to receive radiotherapy. However, it was not possible to distinguish between palliative and radical radiotherapy. Low dose palliative radiotherapy is most commonly given, whereas fewer than 10% of patients receive high dose radiotherapy with potentially-curative intent. It is possible that differential effects by SEP might be seen if these two groups were separated, with more deprived SEP patients more likely to get palliative care, and less deprived patients, curative care. Potentially, these differential effects could cancel each other out and help explain why no overall association was found. However, the low R^2 value [2.98] suggests that the variables in the model do not well account for the factors that are important determinants of receipt of radiotherapy.

10.4.3.4 *Receipt of chemotherapy*

In the multivariable analysis in the subset of patients who had stage recorded, lower SEP was associated with a reduced likelihood of receipt of chemotherapy when including age, sex, histology and stage in the model. However, on the addition of performance status to the model this association was no longer observed, suggesting

that socio-economic differences in performance status may therefore account for the observed socio-economic differences in receipt of chemotherapy in this subgroup. Only two other UK studies [using early LUCADA audit data] have included performance status in a multivariable analysis of receipt of treatment (152, 153). They found that SEP was not associated with receipt of surgery but was associated with receipt of chemotherapy when performance status was included. In contrast we found that, when including performance status, SEP remained associated with a lower likelihood of receipt of surgery but SEP was no longer associated with receipt of chemotherapy in the staged subset. The two previous studies using LUCADA data also found that number of co-morbidities was significantly associated with receipt of surgery but other studies have not found this (157) and nor did this study.

Previous studies used national LUCADA audit data [entered from 2004-2007 and 2004-2008] which, for those early years, included only a small subset of registry patients. Although entry of lung cancer stage data in LUCADA was noted to be 85% complete nationally for 2008 in the Audit report (246), the validity of the 2005 and 2006 LUCADA data has been queried due to the poor entry of staging data (28). In these LUCADA studies no association between SEP and receipt of surgery was found in the unadjusted and adjusted analyses. This result was in contrast to the majority of other UK studies included in a systematic review of inequalities in treatment that found an association between SEP and receipt of surgery (236). It should therefore be queried whether patients included in LUCADA in the early years of the audit are representative of the full spectrum of patients diagnosed with lung cancer in England.

One of the previous LUCADA studies concluded that the data within LUCADA were unbiased and representative of all lung cancer patients in England, despite the variable levels of case ascertainment in the Trusts that supplied data in the early years (153). They also suggested that there was little variation in patient demographics across participating Trusts with different levels of missing data (153), but this does not seem to be quite true. Closer inspection shows that there were significant differences in stage at diagnosis, histology and PS when comparing patients from Trusts with high levels of missing data against those who had low levels of missing data. Patients from Trusts with high levels of missing data were significantly more likely to have early-stage disease but these differences were explained away as being proportionately different

but small at an absolute level (153). Unfortunately SEP was not examined. However, it does appear that results obtained from studies using LUCADA data do differ from those using Registry and HES data, and some caution should be employed when interpreting data from studies using only early-years LUCADA data, as those patients from Trusts with high levels of missing data do appear to be selectively different.

An NCIN report also noted that although concordance of recording of data on receipt of surgery between the combined national registry-HES dataset and the LUCADA dataset was high this was not so for chemotherapy and radiotherapy, with 48% of patients with chemotherapy and 58.6% with radiotherapy recorded in the former having no record in the latter (253), so again this might account for some of the differences seen in my results to that found in previous LUCADA studies.

We were able to include later years of LUCADA data [2009-2010] which are more complete. However, we used local registry data whereas previous studies used England-wide data, which might explain some of the differences observed. Higher levels of missing data for stage and PS were found in our linked dataset than have been reported nationally (246). Higher levels of deprivation are found in the north compared to England as a whole. Although other regional analyses have found inequalities in lung cancer treatment, none have investigated the role of PS and tumour type. It would be useful to perform these analyses using other regional or national registry data to confirm results.

10.4.4 *Implications for policy and practice, and future research*

The results from this study suggest that socio-economic inequalities in performance status substantially explain socio-economic inequalities in receipt of chemotherapy in the subset of patients whose cancer was staged. However, this staged subset may not be representative of the full regional cohort as patients within this were more likely to be younger and of higher SEP. A previous study has shown a socio-economic gradient in completeness of data on stage and grade of cancer, which could be interpreted as inequality in investigative intensiveness (247). It may be that younger patients receive more intensive investigation and so are more likely to be staged (247) and so, although PS may explain inequalities in chemotherapy in this group, they are a selective cohort. This is a relationship that needs to be clarified in other datasets, ideally with lower

levels of missing data for stage and PS. Later years of data in LUCADA have high levels of data completeness and so could be utilised in future.

Guidelines indicate that chemotherapy should be offered to stage III patients and to stage IV patients with good PS [0-1] (18) so that poor PS is a valid reason not to offer chemotherapy to patients who would not be able to tolerate this. Chemotherapy can be offered to patients who are ambulatory and not bed-bound (18). Socio-economic differences in health status may determine whether a patient receives chemotherapy. Patients who do not smoke, eat a healthy and balanced diet, are not overweight or obese, and undertake exercise are more likely to be in better health and so might have a greater chance of being able to undergo chemotherapy. Policy advice regarding healthy lifestyle would therefore apply here, although there is clearly a long chain of causality from health behaviours earlier in life and their specific implications for health status in later life. It is also debateable whether making lifestyle changes once diagnosed with cancer is likely to do much to improve PS, although a recent systematic review and meta-analysis produced preliminary evidence for improved survival [using life table modelling] for early-stage lung cancer patients who quit smoking (254).

A higher percentage of patients in the lowest SEP group had a squamous cell subtype which is strongly associated with smoking. Surgery rates were also lower for this histological subtype. Non-smokers are less likely to get lung cancer and if they do then it appears that they are more likely to get a histological subtype that is more amenable to surgery. This is a further reason, if any other were required, to emphasise why it is important not to smoke. However, we cannot rule out uncontrolled confounding related to smoking-status, where smokers may be less likely to undergo treatment for smoking-related reasons [such as suffering from a serious, smoking-related co-morbidity such as COPD or heart disease] that we cannot measure within this study. Unfortunately smoking status is not recorded in the cancer registry data-set.

This relationship between tumour type and receipt of treatment was not found in a Danish cohort (249) and further UK studies are needed to confirm this association.

I have been able to investigate a number of factors that may be important in the relationship between SEP and receipt of treatment, such as stage and performance status, but the high levels of missing data limit the conclusions that can be drawn.

Although tumour type may account for some of the socio-economic gradient in surgery it does not explain it all. Socio-economic inequalities in PS did not explain inequalities in chemotherapy in the full cohort analyses [although it did within the staged subset], and nor did stage or number of co-morbidities, suggesting that other factors are at play.

I was unable to look at patient choice. Poorer health literacy may influence patient choice and understanding of risk and this may vary by SEP (41). If patients have poor capacity to process and understand basic health information then they are less able to make appropriate health and treatment decisions (43). It is important that clinicians take this into account when discussing treatment options.

Further research is required to investigate the unexplained variance in treatment rates, looking at factors such as patient choice, doctor-patient communication of risk and benefit, and possible system variation by trusts or within this, by hospital and individual consultant. Previous studies have suggested that there may be variation in the level of surgery offered by trusts or, within this, by hospital, so that area-level rather than individual factors may account for treatment variation observed (161). Multi-level modelling is required to fully investigate the effect of area-level factors such as trust, in this data-set.

10.5 Chapter summary

Socio-economic inequalities in receipt of surgery, chemotherapy but not radiotherapy were found in the full cohort analyses.

Socio-economic inequalities in performance status statistically explain socio-economic inequalities in receipt of chemotherapy in the selective subset of patients whose cancer was staged, but not in the full cohort in this study.

Socio-economic inequalities in receipt of surgery cannot be statistically explained by inequalities in stage, PS or co-morbidity. However, socio-economic inequalities in tumour type may account for some of the inequalities in surgery by SEP. Patients in lower SEP groups are more likely to be diagnosed with squamous cell cancer [a tumour type strongly associated with smoking] and are less likely to receive surgery than

patients in higher SEP groups, who are more likely to be diagnosed with adenocarcinoma.

In the next chapter socio-economic inequalities in referral, diagnostic and treatment intervals are examined.

Chapter 11. Inequalities in referral, diagnostic and treatment time intervals

Summary

Background

Diagnostic delay has been implicated as a factor that contributes to the poor survival of UK cancer patients compared to the European average. In England, urgent referrals for suspected cancer are required to have a first hospital appointment [FHA] within 14 days from the date of GP referral [referral interval], and first treatment within 62 days from date of urgent GP referral and within 31 days from diagnosis [treatment intervals]. There has been little work conducted on socio-economic inequalities and delay in lung cancer.

Cancer Registry [NYCRIS], Hospital Episode Statistics [HES] and lung cancer audit [LUCADA] data-sets were linked in order to investigate socio-economic inequalities in system delay for lung cancer.

Methods

System delay was examined in patients diagnosed between 1999 and 2005 [n=36,477] of whom 32,974 [90.4%] had a linked HES record, and in patients diagnosed between 2006 and 2010 [n=28,733] a subset of whom had PS and stage [n=7769, 27.0%] recorded in LUCADA.

Socio-economic inequalities in the likelihood of receipt of referral, diagnosis and treatment within the target intervals and for the calculated interim date targets were explored using logistic regression models. Cox regression analysis was used to examine the influence of SEP on the likelihood of shorter time to first hospital appointment, diagnosis and treatment.

Results (for 2006-2010 cohort)

In the 2006 to 2010 cohort 70% of patients received a hospital appointment within the 14 day referral target. Time to treatment targets were only being met for 42.5% when measured from diagnosis and for 62% from GP referral. Socio-economic inequalities in

time from GP referral to FHA, but not in time to diagnosis or treatment, were found. However no linear trend association between SEP and referral time was found.

Late-stage, poor performance status, and SCLC histology were associated with a higher likelihood of a first hospital appointment within 14 days of GP referral. Older patients were less likely, whereas late stage and poor PS patients were more likely, to receive treatment within guideline time limits.

Conclusions

Patients who appeared sick were more likely to receive early referral, diagnosis and treatment. However, older patients, who were more likely to have poorer PS, were less likely to receive early treatment, indicating possible age-discrimination.

There is some evidence for socio-economic inequalities in the referral but not in the diagnostic or treatment interval. It is possible that the WTP 'sicker quicker' effect may effectively 'cancel out' system inequalities that might result in longer time intervals for lower SEP patients.

11.1 Introduction

Delays between the onset of cancer symptoms and the time to treatment may contribute to the poor survival of UK cancer patients compared to that found in other European countries (99). Early diagnosis of cancer is thought to be important for improving outcomes, as survival is better for patients who are diagnosed at an early stage, because they are more likely to be suitable for receipt of potentially curative treatment (99). Early diagnosis may also result in longer intermediate survival for patients with SCLC and later stage NSCLC [Dr M Peake, *personal communication*].

An early model of cancer delay, the Anderson model [Fig 4.3], attributed the majority of delay to patient rather than system [primary and secondary healthcare] factors. However, it has been suggested that this may be 'an artefact of research focus' and that system delay may be an equally important but under-researched area (102).

Current theoretical models of the pathway from first symptom to cancer treatment identify key intervals and related health care settings (104). Best practice in the definition of key time points demarcating these intervals has also been described (100). In England, three intervals have been the subject of performance management. Since 2000, urgent referrals for suspected cancer have been required to have a first hospital appointment [FHA] within 14 days from the date of referral [referral interval]. Since 2005, intervals of 62 days from date of urgent GP referral to first treatment and 31 days from diagnosis/decision to treat to first treatment [treatment intervals] have been in place (24).

Although some research has been conducted into the factors that might influence delay for some common cancers (105, 112) there has been little work conducted on socio-economic inequalities and delay in lung cancer. Table 4.1 in chapter 4 summarises the current evidence.

In this study cancer registry, Hospital Episode Statistics [HES] and lung cancer audit [LUCADA] data-sets were linked in order to investigate system delay, examining socio-economic inequalities in referral, diagnosis and treatment time for lung cancer patients; the likelihood of referral, diagnosis and treatment within recommended National Cancer Plan [NCP] guideline target times, by SEP; and to examine the other

factors [age, sex, histology, stage, and health status] that may impact on these time intervals.

11.2. Methods

11.2.1 *Data*

For details of data sources and variables see chapter 8, sections 8.2 and 8.4.

11.2.2 *Dates, interval periods and target times*

For details of dates, intervals and target times see chapter 8, table 8.2 and section 8.4.1.

Records were excluded from a particular analysis if they had a negative interval for that time period e.g. if they had a GP referral date later then diagnosis date, as this was likely to be a data entry error. Records were included if they had 0 time between dates [e.g. treatment date was recorded on the same day as date as diagnosis. In order to include these records in the analysis, 0 time intervals were recoded as 0.1].

Analysis was also restricted to those cases with interval dates within one year of the previous interval endpoint. Records were excluded [table 11.1] if the dates fell out-with these timeframes, as extremely long gaps between dates were considered likely to be data entry errors, such as transposition of numbers on date entry. Some patients had very long [one to five year] gaps from GP referral to FHA and these dates might refer to other illness episodes.

Table 11.1. Exclusion of data outliers

Time period	N	N interval > 1 year	% excluded
GP referral to FHA	31415	36	0.11
FHA to diagnosis	31524	20	0.06
Diagnosis to treatment	15051	57	0.38

11.2.3 *Analysis*

NYCRIS data for 28,733 patients diagnosed between 2006 and 2010 and 36,473 diagnosed between 1999 and 2005 were analysed. As date of diagnosis was determined in a different way in 2010 from previous years it was thought that this

might affect calculation of the diagnosis to treatment interval. Therefore inequalities in time from diagnosis to treatment were also examined in the 2006-2009 cohort.

The number and percentage of patients referred within guidelines were calculated and inequalities in the likelihood of receipt of referral, diagnosis and treatment within the targets set by the National Cancer Plan (24) and for the calculated interim date targets [see chapter 8 section 8.4.1.4.2], by SEP, adjusted for age, sex, histology, year of diagnosis, co-morbidity score, stage, and PS, were explored using logistic regression models mutually adjusted for all co-variables. Referral route was also included in the models for the FHA to diagnosis and diagnosis to treatment intervals. Type of first treatment was included in the models for the FHA to treatment and diagnosis to treatment intervals. Receipt of treatment was included in the models for the GP referral to diagnosis and FHA to diagnosis intervals.

Interactions between SEP and histology were also explored. The R^2 statistic was examined to determine the amount of variance in receipt of treatment explained by each model. Odds ratios [ORs] with 95% confidence intervals [CIs] for the likelihood of referral, diagnosis and treatment within target in the lowest compared to the highest SEP group were reported. A likelihood ratio test was performed to determine the overall significance of each categorical variable.

The problem with using logistic regression as described above is that one can only look at the odds of receiving treatment within one year for those who have received **any** treatment, thus excluding around half of the dataset who are untreated. If Cox regression is used, with 'failure' defined as receipt of treatment [equivalent to death in survival analyses, except it is a positive rather than negative outcome], then it is possible to include the whole dataset, even those who did not receive treatment. Hazard ratios [HRs] are a measure of time to treatment in the whole dataset, with a lower hazard ratio equating to a longer time to treatment. This is only relevant for time to treatment analyses as the dates required to calculate time to FHA and diagnosis were well recorded and fairly complete for the whole dataset.

Median time and inter-quartile range [IQR], from GP referral to first hospital appointment [FHA], diagnosis and first treatment, and from diagnosis to treatment, was calculated. Univariable and multivariable Cox regression analysis [with a hazard

ratio of <1.00 indicating longer time to treatment] was used to examine the influence of SEP, adjusted for age, sex, stage, performance status, co-morbidity, histology and year of diagnosis, on the likelihood of shorter time to first hospital appointment, diagnosis and treatment, for those who had dates recorded for those time periods. For some analyses receipt of treatment, type of first treatment and whether the patient had a GP referral date were also included. Hazard ratios [HRs] with 95% confidence intervals [CIs] for the likelihood of early referral, diagnosis and treatment in the lowest compared to the highest SEP group were reported. A likelihood ratio test was performed to determine the overall significance of each categorical variable. Cox regression was also used to assess the likelihood of shorter time to treatment from diagnosis and GP referral date, for the whole dataset, including those who did not receive treatment.

11.3 Results

11.3.1 *Descriptive statistics*

Table 9.1 shows the demographic and clinical characteristics of the lung cancer patients included in the study.

Table 11.2 shows the level of data completeness for diagnosis, FHA and GP referral date and the number receiving treatment. Of the 28,733 patients diagnosed between 2006 and 2010, all had a date of diagnosis, 28, 704 [99.9%] had FHA date recorded, 15,452 [53.8%] had a GP referral date and 15,373 [53.5%] received any treatment within one year of diagnosis. Table 11.3 shows the overall median time per interval compared to target time, and the numbers included in the analysis for each time period.

Table 11.2. Date completeness for 1999-2005 and 2006-2010 data

Date	1999-2005 (n=36,477)		2006-2010 (n=28,733)	
	N	%	N	%
Diagnosis	36,477	100	28,733	100
FHA	36,409	99.8	28,704	99.9
GP referral	16,688	45.7	15,452	53.8
Treatment (any)	19,516	53.5	15,442	53.7
Any treatment within 1 year and with first treatment date >=diagnosis date	19,510	53.5	15,373	53.5

Table 11.3. Median time per interval compared to target time, for 1999-2005 and 2006-2010 data

		1999-2005			2006-2010		
Interval	**Target time***	**N**	**Median time**	**IQR**	**N**	**Median time**	**IQR**
GP referral date to first hospital appointment date	14	16649	10	6-15	14730	10	6-17
GP referral date to diagnosis date	*31*	*16644*	*16*	*9-33*	*14865*	*13*	*7-24*
First hospital appointment date to diagnosis date	*17*	*36330*	*3*	*0-13*	*28284*	*0*	*0-0*
Diagnosis date to first treatment date	31	19510	36	20-62	15373	36	22-56
GP referral date to first treatment date	62	10844	63	41-98	10090	56	39-79

To avoid repetition of results only the results for 2006-2010 are presented below. The pattern of results found was broadly similar in the 1999-2005 cohort [see appendix D tables D1-D3] and for the 2006-2009 dataset [results not shown]. No significant interactions between SEP and histology were found in any of the models.

11.3.2 *GP referral to first hospital appointment 2006-2010*

11.3.2.1 *Hazard ratio of early FHA from GP referral*

Median time from GP referral to FHA was 10 days [IQR 6-17], n=14,730 [table 11.4].

A linear association between SEP and likelihood of earlier FHA within one year of GP referral was not found, although those in the middle SEP groups had significantly decreased likelihood [as measured by HR] of early FHA from referral compared to the least deprived SEP group. Patients with poorer PS, those subsequently diagnosed with later stage cancer and those diagnosed with SCLC all had an increased likelihood [HR] of early FHA from referral in the multivariable analysis [table 11.4]. However, median referral time was between 8-11 days for these variables and so any 'delay' appeared short. Those diagnosed in later years were significantly more likely to have an early FHA with a median time to FHA of 9 days in 2010 compared to 14 days in 2006.

A similar pattern was seen for the cohort that had stage recorded [Appendix D, table D4] although median referral time was shorter in this sub-group [n=5100, median = 9 days (IQR 4-14)].

Table 11.4. Hazard ratio of early first hospital appointment from GP referral (for those referred within 1 year) in 2006-2010 cohort

	FHA	Median time to FHA (days)		Univariable analysis (n=14,730)				Multivariable analysis[1] (n=14,730)			
	N	N	IQR	HR	95% CI		P	HR	95% CI		P
IMD	**14730**	**10**	**6-17**				**0.03**				**0.08**
1 (least deprived)	1735	9	5-15	1.00				1.00			
2	2054	10	6-17	0.94	0.88	1.00	0.05	0.96	0.90	1.02	0.18
3	2496	10	6-17	0.93	0.88	0.99	0.03	0.94	0.88	1.00	0.04
4	3490	11	6-18	0.91	0.86	0.97	0.002	0.93	0.87	0.98	0.008
5 (most deprived)	4955	10	6-17	0.95	0.90	1.01	0.08	0.96	0.91	1.02	0.15
Age Range	**14730**	**10**	**6-17**				**0.004**				**0.004**
<60	2043	10	6-17	1.00				1.00			
60-69	4218	10	6-16	1.01	0.96	1.06	0.75	1.00	0.94	1.05	0.89
70-79	5336	11	6-18	0.94	0.89	0.99	0.02	0.93	0.88	0.98	0.007
80+	3133	10	5-17	0.98	0.92	1.03	0.41	0.96	0.90	1.01	0.13
Sex	**14730**	**10**	**6-17**				**0.36**				**0.96**
Female	6696	10	6-17	1.00				1.00			
Male	8034	10	6-17	0.99	0.95	1.02	0.36	1.00	0.97	1.03	0.96
Histology	**14730**	**10**	**6-17**				**<0.001**				**<0.001**
NSCLC	8940	11	6-18	1.00				1.00			
SCLC	1929	9	5-14	1.20	1.15	1.26	<0.001	1.20	1.14	1.26	<0.001
Other	3861	10	4-17	1.03	0.99	1.07	<0.101	1.02	0.98	1.06	0.28
Year of Diagnosis	**14730**	**10**	**6-17**				**<0.001**				**<0.001**
2006	2498	14	9-25	1.00				1.00			
2007	2603	13	8-21	1.12	1.06	1.19	<0.001	1.12	1.06	1.19	<0.001
2008	3089	8	5-13	1.72	1.63	1.81	<0.001	1.70	1.61	1.79	<0.001
2009	3232	8	3-14	1.69	1.61	1.78	<0.001	1.79	1.67	1.91	<0.001
2010	3308	9	3-14	1.63	1.54	1.71	<0.001	1.69	1.58	1.81	<0.001
Co-morbidity score	**14730**	**10**	**6-17**				**<0.001**				**<0.001**
0	1,929	11	6-19	1.00				1.00			
1-2	1,418	10	4-19	1.02	0.95	1.09	0.56	0.96	0.90	1.03	0.25
3+	298	9	2-20	1.07	0.95	1.21	0.26	0.93	0.82	1.05	0.25
CCM missing	5,432	11	7-19	1.02	0.96	1.07	0.55	1.14	1.08	1.20	<0.001
No HES link	5,653	9	4-14	1.23	1.17	1.30	<0.001	1.00	0.94	1.06	1.00
Stage	**14730**	**10**	**6-17**				**<0.001**				**<0.001**
I	773	11	7-20	1.00				1.00			
II	399	11	5-16	1.21	1.08	1.37	0.002	1.20	1.06	1.35	0.004
III	1578	9	6-15	1.28	1.17	1.39	<0.001	1.23	1.13	1.34	<0.001
IV	2350	8	3-14	1.47	1.36	1.60	<0.001	1.36	1.25	1.48	<0.001
Missing/ unknown	9630	11	6-19	1.08	1.00	1.16	0.04	1.21	1.11	1.32	<0.001
Performance Status	**14730**	**10**	**6-17**				**<0.001**				**<0.001**
0	1,367	11	6-15	1.00				1.00			
1-2	3,257	9	5-15	1.07	1.01	1.14	0.03	1.05	0.99	1.12	0.13
3-4	1,230	7	0-13	1.39	1.28	1.50	<0.001	1.33	1.23	1.44	<0.001
Missing/ unknown	8,876	11	6-19	0.91	0.86	0.96	0.001	1.01	0.94	1.08	0.88

[1] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, stage, PS

Table 11.5. Odds of FHA within 14 days from GP referral (for those with FHA within 1 year of GP ref) 2006-2010

	FHA within 1 year	FHA within 14 days		Univariable analysis (n=14,730)				Multivariable analysis[1] (n=14,730, R^2=6.80)			
	N	N	%	OR	95% CI		P	OR	95% CI		P
IMD	**14730**	**10319**	**70.1**				**0.005**				**0.001**
1 (least deprived)	1735	1274	73.4	1.00				1.00			
2	2054	1439	70.1	0.85	0.73	0.98	0.02	0.85	0.74	0.99	0.04
3	2496	1738	69.6	0.83	0.72	0.95	0.007	0.81	0.70	0.93	0.003
4	3490	2385	68.3	0.78	0.69	0.89	<0.001	0.75	0.66	0.86	<0.001
5 (most deprived)	4955	3483	70.3	0.86	0.76	0.97	0.01	0.83	0.73	0.94	0.004
Age Range	**14730**	**10319**	**70.1**				**0.01**				**0.03**
<60	2043	1467	71.8	1.00				1.00			
60-69	4218	3005	71.2	0.97	0.87	1.09	0.64	0.96	0.85	1.08	0.49
70-79	5336	3661	68.6	0.86	0.77	0.96	0.008	0.86	0.76	0.97	0.01
80+	3133	2186	69.8	0.91	0.80	1.02	0.12	0.89	0.78	1.02	0.09
Sex	**14730**	**10319**	**70.1**				**0.17**				**0.80**
Female	6696	4729	70.6	1.00				1.00			
Male	8034	5590	69.6	0.95	0.89	1.02	0.17	1.01	0.94	1.09	0.80
Histology	**14730**	**10319**	**70.1**				**<0.001**				**<0.001**
NSCLC	8940	6135	68.6	1.00				1.00			
SCLC	1929	1492	77.4	1.56	1.39	1.75	<0.001	1.62	1.43	1.83	<0.001
Other	3861	2692	69.7	1.05	0.97	1.14	0.22	1.04	0.95	1.14	0.42
Year of Diagnosis	**14730**	**10319**	**70.1**				**<0.001**				**<0.001**
2006	2498	1250	50.0	1.00				1.00			
2007	2603	1484	57.0	1.32	1.19	1.48	<0.001	1.33	1.19	1.49	<0.001
2008	3089	2491	80.6	4.16	3.69	4.68	<0.001	4.17	3.69	4.70	<0.001
2009	3232	2543	78.7	3.68	3.28	4.13	<0.001	4.24	3.66	4.91	<0.001
2010	3308	2551	77.1	3.36	3.01	3.77	<0.001	3.80	3.26	4.43	<0.001
Co-morbidity score	**14730**	**10319**	**70.1**				**<0.001**				**<0.001**
0	1,929	1,291	66.9	1.00				1.00			
1-2	1,418	956	67.4	1.02	0.88	1.18	0.76	0.91	0.78	1.06	0.23
3+	298	204	68.5	1.07	0.83	1.39	0.60	0.82	0.62	1.08	0.17
CCM missing	5,432	3,577	65.9	0.95	0.85	1.06	0.39	1.25	1.10	1.41	<0.001
No HES link	5,653	4,291	75.9	1.56	1.39	1.74	<0.001	0.95	0.83	1.09	0.46
Stage	**14730**	**10319**	**70.1**				**<0.001**				**<0.001**
I	773	508	65.7	1.00				1.00			
II	399	286	71.7	1.32	1.01	1.72	0.04	1.33	1.01	1.75	0.04
III	1578	1182	74.9	1.56	1.29	1.88	<0.001	1.50	1.24	1.83	<0.001
IV	2350	1870	79.6	2.03	1.70	2.43	<0.001	1.74	1.44	2.10	<0.001
Missing/ unknown	9630	6473	67.2	1.07	0.92	1.25	0.39	1.42	1.17	1.72	<0.001
Performance Status	**14730**	**10319**	**70.1**				**<0.001**				**0.0005**
0	1,367	997	72.9	1.00				1.00			
1-2	3,257	2,422	74.4	1.08	0.93	1.24	0.31	1.01	0.87	1.18	0.88
3-4	1,230	998	81.1	1.60	1.33	1.92	<0.001	1.38	1.13	1.69	<0.001
Missing/ unknown	8,876	5,902	66.5	0.74	0.65	0.84	<0.001	0.94	0.80	1.12	0.49

[1] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, stage, PS

11.3.2.2 *Likelihood of FHA within 14 days of GP referral*

Of those referred by their GP [which could include both urgent and non-urgent referrals], 70.1% had a first hospital appointment within 2 weeks of referral.

Low SEP was associated with a lower likelihood of FHA within 2 weeks of referral in the multivariable analysis [OR=0.83, CI 0.73 to 0.94, p=0.004] but the lowest likelihood was for those in the middle SEP groups. A similar pattern was seen for the 1999-2005 cohort [Appendix D, table D1]. Late stage cancer, SCLC, poor performance status and referral post-2006 were associated with increased likelihood of FHA within 14 days of referral, but older age [80+], sex and number of co-morbidities were not [table 11.5].

11.3.3 *GP referral to diagnosis 2006-2010*

11.3.3.1 *Hazard ratio of early diagnosis from GP referral*

In those patients with GP referral and diagnosis dates [n=14,860] median time from GP referral to diagnosis was 13 days [IQR 7-24].

Similarly to the pattern seen in the GP referral to FHA interval, those in the middle SEP groups had the lowest likelihood of earlier diagnosis. Patients with poorer PS, co-morbidities, those subsequently diagnosed with later stage cancer and those with SCLC had an increased likelihood [HR] of early diagnosis [table 11.6]. Those who subsequently went on to receive treatment had longer median time to diagnosis. Similar results were seen for the cohort subset [n=5148] who had stage recorded [data not shown].

11.3.3.2 *Likelihood of diagnosis within 31 days of GP referral*

Neither SEP nor age was associated with likelihood of diagnosis within 31 days of GP referral overall, although those in the middle SEP groups had significantly lower likelihood of diagnosis within 31 days [table 11.7]. Patients with poorer PS, later stage cancer and those with SCLC had an increased likelihood of diagnosis within 31 days of GP referral. Those diagnosed in in 2007-2009 appeared to have a higher likelihood of diagnosis within 31 days compared to those diagnosed in 2010. However, similar overall results were seen for the 2006-2009 data-set [results not shown].

11.3.4 Diagnosis to first treatment 2006-2010

11.3.4.1 *Hazard ratio of early treatment for those treated within 1 year of diagnosis*

Median time from diagnosis to first treatment was 36 days [IQR 22-56], for the 15,373 patients who had first treatment within 1 year of diagnosis [table 11.8].

No association between SEP and likelihood [HR] of early treatment was found. Patients with late stage cancer, those with SCLC and those with poor performance status were more likely to receive early treatment.

Older patients had longer time to treatment [median time to treatment was 41 days for those aged 80+ compared to 33 days for those aged <60].

Patients with stage 1 lung cancer waited a median of 51 days for treatment, whereas those with stage 4 cancer waited 30 days. This may reflect the type of treatment they were likely to receive as patients who received surgery as a first treatment had a median waiting time 17 days longer than patients who received chemotherapy and 10 days longer than those who had radiotherapy first. Patients with poor performance status waited a median of 28 days to treatment compared with 37 days for those with good performance status. No clear pattern of waiting time was seen for number of co-morbidities, however. For those treated in 2010 it appeared that time to treatment was shorter than in all other years [median =29 days compared to 35-41 days in other years]. Again this may be related to how date of diagnosis was calculated in this year.

11.3.4.2 *Hazard ratio of early treatment from diagnosis for entire cohort, including untreated*

I also examined the likelihood of receiving early treatment for the whole dataset, including those who did not receive treatment [table 11.9]. Using this whole-dataset methodology resulted in some contrasting findings compared to including only those who received treatment.

Those with low SEP were significantly less likely to receive early treatment in the lowest compared to the highest SEP group [HR=0.83, CI 0.79 to 0.88), p<0.001], as were those with co-morbidities. Those with later stage cancer were less likely to receive earlier treatment, as were those with poorer performance status whereas the

reverse was found in the treatment-only cohort. Those referred via the GP were more likely to receive early treatment and, again, the reverse was found in the treatment-only cohort. Older patients were significantly less likely to receive early treatment as were those with co-morbidities. Those diagnosed with SCLC were more likely to receive early treatment.

11.3.4.3 *Likelihood of treatment within 31 day of diagnosis*

Of the 15,373 patients who were treated within one year, 42.5% [6,537] were treated within the 31 day target time from diagnosis [table 11.10].

There was no association between low SEP and likelihood of treatment within 31 days [OR=0.91, CI 0.81 to 1.02, p=0.11], for those treated within 1 year of diagnosis.

Although 73.4% of SCLC patients were treated within target, this was true for only 35.4% of NSCLC patients. Histology appeared the most important factor in the likelihood of receiving timely treatment, with a median time of 22 days for SCLC compared to 40 days for NSCLC. Patients with SCLC often deteriorate quickly and need to receive chemotherapy as soon as possible within a short 'window of opportunity' to improve survival time.

Older patients were significantly less likely to receive treatment within the 31 day target even when factors such as stage and PS were taken into account [OR=0.78, CI 0.68 to 0.89, p<0.001]. The type of treatment first received also influenced the likelihood of treatment within target. Those receiving surgery were less likely to receive treatment within target times. Those with poor performance status and those receiving chemotherapy were more likely to do so.

11.3.5 GP referral to first treatment 2006-2010

11.3.5.1 *Hazard ratio of early treatment from GP referral*

Median time from GP referral to first treatment date was 56 days [IQR 39-79] in the 10,090 patients who had both dates recorded [table 11.11]. Patients in the middle and low SEP groups were less likely to receive early treatment compared to the highest SEP group.

Early stage patients, older patients and those receiving surgery were significantly less likely to receive early treatment, whereas later stage patients, those with poor performance status and those receiving chemotherapy as first treatment were more likely to do so.

11.3.5.2 *Likelihood of treatment within 62 days of GP referral*

61.8% of those who received treatment were treated within the 62 day target from GP referral [although this could include patients who were not urgently referred] [table 11.12]. No linear trend association between SEP and likelihood of starting treatment within the target time was found [p=0.08] although those in the middle SEP groups were significantly less likely to start treatment within 62 days.

Early stage patients, older patients and those receiving surgery were significantly less likely to start treatment within 62 days, whereas late stage patients, those with poor PS and those receiving chemotherapy were more likely to do so. The likelihood of receiving treatment within guidelines significantly improved over time.

Table 11.6. Hazard ratio of early diagnosis (for those referred by GP within 1 year and with diagnosis date within 1 year from FHA), for 2006 to 2010 cohort

Variable	Diagnosis	Median time to diagnosis (days)		Univariable analysis (n=14,860)				Multivariable analysis[1] (n=14,860)			
	N	N	IQR	HR	95% CI		P	HR	95% CI		P
IMD	**14,860**	**13**	**7-24**				**0.04**				**0.04**
1 (least deprived)	1,746	13	7-21	1.00				1.00			
2	2,074	13	7-24	0.93	0.87	0.99	0.02	0.94	0.88	1.00	0.07
3	2,519	13	7-25	0.91	0.86	0.97	0.004	0.92	0.86	0.97	0.005
4	3,521	14	7-25	0.93	0.88	0.98	0.01	0.92	0.87	0.98	0.005
5 (most deprived)	5,000	13	7-23	0.95	0.90	1.00	0.04	0.95	0.90	1.00	0.06
Age Range	**14,860**	**13**	**7-24**				**0.03**				**0.04**
<60	2,064	13	7-23	1.00				1.00			
60-69	4,252	13	7-23	1.00	0.95	1.05	0.97	1.01	0.96	1.07	0.70
70-79	5,394	14	7-24	0.96	0.92	1.01	0.16	0.95	0.91	1.01	0.08
80+	3,150	13	7-23	1.03	0.97	1.09	0.34	0.97	0.91	1.03	0.30
Sex	**14,860**	**13**	**7-24**				**0.88**				**0.63**
Female	6,760	13	7-24	1.00				1.00			
Male	8,100	13	7-23	1.00	0.97	1.03	0.88	1.01	0.98	1.04	0.63
Histology	**14,860**	**13**	**7-24**				**<0.001**				**<0.001**
NSCLC	9,027	14	8-25	1.00				1.00			
SCLC	1,942	12	7-19	1.28	1.22	1.34	<0.001	1.27	1.21	1.34	<0.001
Other	3,891	12	6-22	1.11	1.07	1.16	<0.001	1.06	1.01	1.10	0.01
Year of diagnosis	**14,860**	**13**	**7-24**				**<0.001**				**<0.001**
2006	2,501	16	9-28	1.00				1.00			
2007	2,601	14	8-24	1.15	1.09	1.22	<0.001	1.15	1.08	1.21	<0.001
2008	3,140	11	6-18	1.49	1.41	1.57	<0.001	1.45	1.38	1.53	<0.001
2009	3,260	10	5-19	1.51	1.43	1.59	<0.001	1.62	1.52	1.73	<0.001
2010	3,358	16	8-30	1.01	0.96	1.06	0.81	1.07	1.00	1.14	0.07
Co-morbidity score	**14,860**	**13**	**7-24**				**<0.001**				**<0.001**
0	1,958	14	7-26	1.00				1.00			
1-2	1,430	13	7-27	1.00	0.93	1.07	0.89	0.94	0.88	1.01	0.10
3+	303	13	5-29	0.93	0.83	1.05	0.27	0.84	0.74	0.95	0.006
CCM missing	5,464	13	7-21	1.13	1.08	1.19	<0.001	1.20	1.14	1.27	<0.001
No HES link	5,705	14	7-25	1.05	1.00	1.11	0.05	1.02	0.96	1.08	0.46
Stage	**14,860**	**13**	**7-24**				**<0.001**				**<0.001**
I	783	18	10-37	1.00				1.00			
II	403	16	8-28	1.18	1.04	1.33	0.008	1.21	1.08	1.37	0.002
III	1,592	13	7-22	1.45	1.33	1.58	<0.001	1.38	1.27	1.51	<0.001
IV	2,369	11	5-19	1.77	1.64	1.92	<0.001	1.64	1.51	1.78	<0.001
Missing/ unknown	9,713	13	7-24	1.34	1.24	1.44	<0.001	1.29	1.19	1.41	<0.001
Performance Status	**14,860**	**13**	**7-24**				**<0.001**				**<0.001**
0	1,376	14	8-27	1.00				1.00			
1-2	3,287	13	7-23	1.14	1.07	1.21	<0.001	1.08	1.01	1.15	0.02
3-4	1,240	8	3-17.5	1.54	1.43	1.66	<0.001	1.33	1.23	1.44	<0.001
Missing/ unknown	8,957	14	7-24	1.07	1.01	1.13	0.03	1.05	0.98	1.13	0.18
Any treatment	**14,860**	**13**	**7-24**				**<0.001**				**<0.001**
No	5063	12	6-21					1.00			
Yes	9767	14	8-25	0.84	0,82	0.88	<0.001	0.89	0.85	0.93	<0.001

[1] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, stage, PS, any treatment

Table 11.7. Odds of diagnosis within 31 days of GP referral (excluding those with FHA > 1 year from GP ref and diagnosis> 1 year from FHA) 2006-2010

	Diagnosis within 2 years	Diagnosis within 31 days		Univariable analysis (n=14,860)				Multivariable analysis[1] (n=14,860, R^2=4.68)			
	N	N	%	OR	95% CI		P	OR	95% CI		P
IMD	**14,860**	**12,287**	**82.7**				**0.22**				**0.11**
1 (least deprived)	1,746	1,469	84.1	1.00				1.00			
2	2,074	1,710	82.5	0.89	0.75	1.05	0.17	0.90	0.76	1.07	0.25
3	2,519	2,061	81.8	0.85	0.72	1.00	0.05	0.84	0.71	0.99	0.04
4	3,521	2,889	82.1	0.86	0.74	1.01	0.06	0.83	0.71	0.97	0.02
5 (most deprived)	5,000	4,158	83.2	0.93	0.80	1.08	0.35	0.93	0.80	1.08	0.32
Age Range	**14,860**	**12,287**	**82.7**				**0.57**				**0.37**
<60	2,064	1,705	82.6	1.00				1.00			
60-69	4,252	3,535	83.1	1.04	0.90	1.19	0.60	1.07	0.93	1.24	0.33
70-79	5,394	4,431	82.2	0.97	0.85	1.11	0.64	0.98	0.85	1.12	0.74
80+	3,150	2,616	83.1	1.03	0.89	1.19	0.68	0.98	0.83	1.15	0.81
Sex	**14,860**	**12,287**	**82.7**				**0.09**				**0.009**
Female	6,760	5,550	82.1	1.00				1.00			
Male	8,100	6,737	83.2	1.08	0.99	1.17	0.09	1.12	1.03	1.23	0.009
Histology	**14,860**	**12,287**	**82.7**				**<0.001**				**<0.001**
NSCLC	9,027	7,330	81.2	1.00				1.00			
SCLC	1,942	1,714	88.3	1.74	1.50	2.02	<0.001	1.76	1.51	2.05	<0.001
Other	3,891	3,243	83.4	1.16	1.05	1.28	0.004	1.04	0.93	1.17	0.47
Year of Diagnosis	**14,860**	**12,287**	**82.7**				**<0.001**				**<0.001**
2006	2,501	1,925	77.0	1.00				1.00			
2007	2,601	2,159	83.0	1.46	1.27	1.68	<0.001	1.47	1.28	1.70	<0.001
2008	3,140	2,782	88.6	2.33	2.01	2.69	<0.001	2.29	1.98	2.65	<0.001
2009	3,260	2,853	87.5	2.10	1.82	2.41	<0.001	2.44	2.06	2.90	<0.001
2010	3,358	2,568	76.5	0.97	0.86	1.10	0.66	1.04	0.88	1.24	0.64
Co-morbidity score	**14,860**	**12,287**	**82.7**				**<0.001**				**<0.001**
0	1,958	1,575	80.4	1.00				1.00			
1-2	1,430	1,137	79.5	0.94	0.80	1.12	0.50	0.86	0.73	1.03	0.11
3+	303	229	75.6	0.75	0.57	1.00	0.05	0.67	0.50	0.90	0.008
CCM missing	5,464	4,664	85.4	1.42	1.24	1.62	<0.001	1.53	1.33	1.77	<0.001
No HES link	5,705	4,682	82.1	1.11	0.98	1.27	0.11	1.12	0.96	1.31	0.14
Stage	**14,860**	**12,287**	**82.7**				**<0.001**				**<0.001**
I	783	553	70.6	1.00				1.00			
II	403	312	77.4	1.43	1.08	1.89	0.01	1.53	1.15	2.04	0.003
III	1,592	1,343	84.4	2.24	1.83	2.75	<0.001	2.11	1.71	2.61	<0.001
IV	2,369	2,111	89.1	3.40	2.78	4.16	<0.001	2.93	2.38	3.62	<0.001
Missing/ unknown	9,713	7,968	82.0	1.90	1.61	2.23	<0.001	1.64	1.33	2.03	<0.001
Performance Status	**14,860**	**12,287**	**82.7**				**<0.001**				**0.005**
0	1,376	1,089	79.1	1.00				1.00			
1-2	3,287	2,754	83.8	1.36	1.16	1.60	<0.001	1.23	1.04	1.45	0.02
3-4	1,240	1,107	89.3	2.19	1.76	2.74	<0.001	1.66	1.30	2.12	<0.001
Missing/ unknown	8,957	7,337	81.9	1.19	1.04	1.37	0.01	1.19	0.98	1.44	0.08
Any treatment	**14,860**	**12,287**	**82.7**								**<0.001**
No	5,063	4,328	85.5	1.00				1.00			
Yes	9,797	7,959	81.2	0.74	0.67	0.81	<0.001	0.75	0.66	0.84	<0.001

[1] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, stage, PS, any treatment

Table 11.8. HR of early treatment from diagnosis (for those treated within 1 year of diagnosis and excluding those untreated) 2006 to 2010

	Treated	Median time to treatment (days)		Univariable analysis (n=15,373)				Multivariable analysis[1] (n=15,373)			
	N	N	IQR	HR	95% CI		P	HR	95% CI		P
IMD	**15,373**	**36**	**22-56**				**0.70**				**0.25**
1 (least deprived)	1,928	35	21-55	1.00				1.00			
2	2,298	35	21-56	1.00	0.94	1.06	0.89	1.00	0.94	1.06	0.95
3	2,605	36	22-57	0.98	0.92	1.03	0.41	0.97	0.92	1.03	0.35
4	3,510	36	22-56	0.97	0.91	1.02	0.22	0.95	0.90	1.00	0.07
5 (most deprived)	5,032	36	22-56	0.98	0.93	1.03	0.38	0.97	0.92	1.02	0.25
Age Range	**15,373**	**36**	**22-56**				**<0.001**				**<0.001**
<60	2,941	33	20-50	1.00				1.00			
60-69	5,322	35	21-54	0.93	0.89	0.97	0.002	0.96	0.92	1.01	0.10
70-79	5,360	38	23-61	0.79	0.75	0.82	<0.001	0.84	0.80	0.88	<0.001
80+	1,750	41	23-61	0.74	0.70	0.79	<0.001	0.86	0.81	0.92	<0.001
Sex	**15,373**	**36**	**22-56**				**<0.001**				**0.07**
Female	6,918	35	21-55	1.00				1.00			
Male	8,455	36	22-57	0.94	0.91	0.97	<0.001	0.97	0.94	1.00	0.07
Histology	**15,373**	**36**	**22-56**				**<0.001**				**<0.001**
NSCLC	10,638	40	26-59	1.00				1.00			
SCLC	2,615	22	14-33	2.17	2.08	2.27	<0.001	1.96	1.87	2.05	<0.001
Other	2,120	38.5	20-64	0.94	0.89	0.98	0.005	0.98	0.94	1.03	0.45
Diagnosis year	**15,373**	**36**	**22-56**				**<0.001**				**<0.001**
2006	2956	35	21-54	1.00				1.00			
2007	3006	36	22-57	0.96	0.92	1.01	0.15	0.95	0.90	1.00	0.06
2008	3010	41	25-62	0.87	0.82	0.91	<0.001	0.83	0.79	0.88	<0.001
2009	3262	40	24-60	0.89	0.85	0.94	<0.001	0.88	0.83	0.94	<0.001
2010	3139	29	16-46	1.25	1.19	1.32	<0.001	1.26	1.17	1.35	<0.001
Co-morbidity score	**15,373**	**36**	**22-56**				**<0.001**				**0.34**
0	2,323	37	22-57	1.00				1.00			
1-2	1,617	40	24-63	0.93	0.87	0.99	0.02	0.94	0.89	1.01	0.08
3+	352	37.5	20-69	0.92	0.82	1.02	0.12	0.98	0.87	1.09	0.68
CCM missing	5,996	36	22-56	1.02	0.97	1.07	0.40	1.00	0.95	1.05	0.96
No HES link	5,085	34	20-52	1.11	1.06	1.17	<0.001	0.97	0.91	1.03	0.32
GP referral date	**15,373**	**36**	**22-56**				**0.28**				**0.21**
No	5,253	35	19-58	1.00				1.00			
Yes	10,120	36	23-55	1.01	0.99	1.05	0.28	1.02	0.99	1.06	0.21
Stage	**15,373**	**36**	**22-56**				**<0.001**				**<0.001**
I	922	51	32-74	1.00				1.00			
II	403	48	32-69	1.07	0.95	1.20	0.27	1.00	0.89	1.12	0.95
III	1,602	39	27-57	1.33	1.22	1.44	<0.001	1.16	1.07	1.26	0.001
IV	2,009	30	20-44	1.84	1.70	1.99	<0.001	1.52	1.40	1.65	<0.001
Missing/ unknown	10,437	35	21-56	1.37	1.28	1.47	<0.001	1.30	1.20	1.41	<0.001
Performance Status	**15,373**	**36**	**22-56**				**<0.001**				**<0.001**
0	1,673	37	24-57	1.00				1.00			
1-2	3,594	35	22-54	1.05	0.99	1.11	0.11	1.06	1.00	1.13	0.05
3-4	466	28	15-48	1.27	1.15	1.41	<0.001	1.31	1.18	1.46	<0.001
Missing/ unknown	9,640	36	21-57	0.97	0.92	1.02	0.23	0.95	0.88	1.01	0.12
Ist treatment	**15,373**	**36**	**22-56**				**<0.001**				**<0.001**
Chemotherapy	6863	30	21-45	1.00				1.00			
Surgery	2830	47	20-68	0.65	0.62	0.68	0.65	0.83	0.79	0.87	<0.001
Radiotherapy	5680	40	24-63	0.64	0.62	0.67	0.64	0.75	0.73	0.79	<0.001

[1] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, stage, PS, first treatment

Table 11.9. Hazard ratio of early treatment for 2006-2010 cohort, including those who did not receive treatment, looking at time from diagnosis to first treatment (n treated =15,373)

	Univariable analysis (n=28,664)				Multivariable analysis[1] (n=28,664)				Multivariable analysis[2] (n=28,664)			
	HR	**95% CI**		**P**	**HR**	**95% CI**		**P**	**HR**	**95% CI**		**P**
IMD				**<0.001**				**<0.001**				**<0.001**
1 (least deprived)	1.00				1.00				1.00			
2	0.96	0.90	1.01	0.14	0.95	0.90	1.01	0.13	0.95	0.89	1.01	0.09
3	0.91	0.86	0.97	0.003	0.90	0.85	0.95	<0.001	0.91	0.86	0.96	0.002
4	0.88	0.83	0.93	<0.001	0.84	0.80	0.89	<0.001	0.85	0.80	0.90	<0.001
5 (most deprived)	0.88	0.83	0.93	<0.001	0.82	0.78	0.86	<0.001	0.83	0.79	0.88	<0.001
Age Range				**<0.001**				**<0.001**				**<0.001**
<60	1.00				1.00				1.00			
60-69	0.76	0.73	0.79	<0.001	0.81	0.78	0.85	<0.001	0.82	0.78	0.86	<0.001
70-79	0.47	0.45	0.49	<0.001	0.57	0.54	0.59	<0.001	0.58	0.56	0.61	<0.001
80+	0.18	0.17	0.19	<0.001	0.29	0.27	0.31	<0.001	0.31	0.29	0.32	<0.001
Sex				**0.002**				**0.21**				**0.29**
Female	1.00				1.00				1.00			
Male	1.05	1.02	1.09	0.002	0.98	0.95	1.01	0.21	0.98	0.95	1.01	0.29
Histology				**<0.001**				**<0.001**				**<0.001**
NSCLC	1.00				1.00				1.00			
SCLC	1.50	1.44	1.57	<0.001	1.55	1.49	1.62	<0.001	1.64	1.57	1.72	<0.001
Other	0.21	0.20	0.22	<0.001	0.30	0.28	0.31	<0.001	0.33	0.31	0.34	<0.001
Diagnosis year				**<0.001**				**<0.001**				**<0.001**
2006	1.00				1.00				1.00			
2007	0.97	0.92	1.02	0.20	0.98	0.93	1.03	0.35	0.97	0.92	1.02	0.24
2008	0.91	0.87	0.96	0.00	0.88	0.83	0.92	<0.001	0.86	0.82	0.91	<0.001
2009	1.02	0.97	1.07	0.39	1.14	1.07	1.22	<0.001	1.10	1.03	1.17	0.004
2010	1.09	1.04	1.15	0.00	1.37	1.28	1.47	<0.001	1.35	1.26	1.44	<0.001
Co-morbidity score				**<0.001**				**<0.001**				**<0.001**
0	1.00				1.00				1.00			
1-2	0.71	0.66	0.75	<0.001	0.85	0.80	0.91	<0.001	0.86	0.81	0.92	<0.001
3+	0.56	0.50	0.62	<0.001	0.75	0.67	0.84	<0.001	0.77	0.69	0.86	<0.001
CCM missing	1.03	0.98	1.08	0.27	1.00	0.95	1.05	1.00	1.01	0.96	1.06	0.76
No HES link	0.84	0.80	0.89	<0.001	0.77	0.73	0.82	<0.001	0.78	0.74	0.83	<0.001
GP referral				**<0.001**				**<0.001**				**<0.001**
No	1.00				1.00				1.00			
Yes	2.02	1.95	2.09	<0.001	1.64	1.58	1.70	<0.001	1.58	1.52	1.63	<0.001
Stage				**<0.001**								**<0.001**
I	1.00								1.00			
II	0.92	0.82	1.04	0.17					0.85	0.75	0.95	0.005
III	0.94	0.87	1.02	0.16					0.87	0.80	0.95	0.001
IV	0.68	0.63	0.73	<0.001					0.78	0.72	0.85	<0.001
Missing/unknown	0.58	0.54	0.62	<0.001					0.84	0.77	0.91	<0.001
Performance Status				**<0.001**								**<0.001**
0	1.00								1.00			
1-2	0.70	0.66	0.74	<0.001					0.90	0.85	0.96	0.001
3-4	0.13	0.12	0.15	<0.001					0.27	0.24	0.30	<0.001
Missing/ unknown	0.36	0.34	0.38	<0.001					0.65	0.61	0.70	<0.001

[1] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, GP referral

[2] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, GP referral, stage, PS

Table 11.10. Odds of receiving any treatment within 31 days of diagnosis (for those treated within 1 year of diagnosis) 2006-10

	Treated	Treated within 31 days		Univariable analysis (n=15,373)				Multivariable analysis[1] (n=15,373, R^2=9.43)			
	N	N	%	OR	95% CI		P	OR	95% CI		P
IMD	**15,373**	**6,537**	**42.5**				**0.39**				**0.29**
1 (least deprived)	1,928	849	44.0	1.00				1.00			
2	2,298	993	43.2	0.97	0.86	1.09	0.59	0.97	0.85	1.11	0.67
3	2,605	1,089	41.8	0.91	0.81	1.03	0.13	0.89	0.78	1.01	0.06
4	3,510	1,504	42.9	0.95	0.85	1.07	0.40	0.94	0.84	1.06	0.34
5 (most deprived)	5,032	2,102	41.8	0.91	0.82	1.01	0.09	0.91	0.81	1.02	0.11
Age Range	**15,373**	**6,537**	**42.52**				**<0.001**				**<0.001**
<60	2,941	1,409	47.9	1.00				1.00			
60-69	5,322	2,355	44.3	0.86	0.79	0.94	0.001	0.89	0.81	0.98	0.02
70-79	5,360	2,111	39.4	0.71	0.65	0.77	<0.001	0.75	0.68	0.83	<0.001
80+	1,750	662	37.8	0.66	0.59	0.75	<0.001	0.78	0.68	0.89	<0.001
Sex	**15,373**	**6,537**	**42.5**				**0.001**				**0.27**
Female	6,918	3,045	44.0	1.00				1.00			
Male	8,455	3,492	41.3	0.89	0.84	0.95	0.001	0.96	0.90	1.03	0.27
Histology	**15,373**	**6,537**	**42.5**				**<0.001**				**<0.001**
NSCLC	10,638	3,765	35.4	1.00				1.00			
SCLC	2,615	1,920	73.4	5.04	4.58	5.55	<0.001	4.38	3.94	4.86	<0.001
Other	2,120	852	40.2	1.23	1.11	1.35	<0.001	1.26	1.14	1.39	<0.001
Co-morbidity score	**15,373**	**6,537**	**42.5**				**<0.001**				**0.24**
0	2,323	940	40.5	1.00				1.00			
1-2	1,617	598	37.0	0.86	0.76	0.98	0.03	0.91	0.79	1.04	0.17
3+	352	145	41.2	1.03	0.82	1.29	0.80	1.08	0.85	1.38	0.52
CCM missing	5,996	2,482	41.4	1.04	0.94	1.15	0.44	1.02	0.92	1.14	0.68
No HES link	5,085	2,372	46.7	1.29	1.16	1.42	<0.001	1.05	0.92	1.19	0.46
Diagnosis year	**15,373**	**6,537**	**42.5**				**<0.001**				**<0.001**
2006	2,956	1,314	44.5	1.00				1.00			
2007	3,006	1,250	41.6	0.89	0.80	0.99	0.03	0.88	0.79	0.98	0.02
2008	3,010	1,071	35.6	0.69	0.62	0.77	<0.001	0.64	0.57	0.71	<0.001
2009	3,262	1,196	36.7	0.72	0.65	0.80	<0.001	0.68	0.59	0.79	<0.001
2010	3,139	1,706	54.4	1.49	1.34	1.65	<0.001	1.54	1.32	1.79	<0.001
GP referral	**15,373**	**6,537**	**42.5**				**<0.001**				**<0.001**
No GP referral	5,253	2,384	45.4	1.00				1.00			
FHA<=14 days	7,178	3,081	42.9	0.91	0.84	0.97	0.006	0.89	0.83	0.97	0.006
FHA >14 days	2,942	1,072	36.4	0.69	0.63	0.76	<0.001	0.73	0.66	0.81	<0.001
1st treatment	**15,373**	**6,537**	**42.5**								**<0.001**
Chemotherapy	6,863	3,563	51.9	1.00				1.00			
Surgery	2,830	903	31.9	0.43	0.40	0.48	<0.001	0.77	0.69	0.86	<0.001
Radiotherapy	5,680	2,071	36.5	0.53	0.49	0.57	<0.001	0.77	0.71	0.84	<0.001
Stage	**15,373**	**6,537**	**42.5**				**<0.001**				**<0.001**
I	922	229	24.8	1.00				1.00			
II	403	98	24.3	0.97	0.74	1.28	0.84	0.86	0.65	1.14	0.28
III	1,602	580	36.2	1.72	1.43	2.06	<0.001	1.33	1.09	1.61	0.005
IV	2,009	1,065	53.0	3.41	2.87	4.06	<0.001	2.48	2.05	3.00	<0.001
Missing/unknown	10,437	4,565	43.7	2.35	2.02	2.75	<0.001	1.77	1.45	2.14	<0.001
Performance Status	**15,373**	**6,537**	**42.5**				**<0.001**				**0.0001**
0	1,673	647	38.7	1.00				1.00			
1-2	3,594	1,551	43.2	1.20	1.07	1.36	0.002	1.10	0.96	1.25	0.15
3-4	466	256	54.9	1.93	1.57	2.38	<0.001	1.68	1.33	2.12	<0.001
Missing/ unknown	9,640	4,083	42.4	1.17	1.05	1.30	0.005	1.01	0.87	1.17	0.92

[1] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, GP referral, 1st treatment, stage, PS

Table 11.11. HR of early treatment from GP referral (for those treated within 1 year of diagnosis and excluding those untreated) 2006 to 2010

	Treatment	Median time to treatment (days)		Univariable analysis (n=10,090)				Multivariable analysis[1] (n=10,090)			
	N	N	IQR	HR	95% CI		P	HR	95% CI		P
MD	**10,090**	**56**	**39-79**				**0.09**				**0.049**
1 (least deprived)	1,250	54	36-75	1.00				1.00			
2	1,460	55	38-79	0.94	0.87	1.01	0.10	0.95	0.88	1.03	0.22
3	1,696	56	39-80.5	0.92	0.85	0.99	0.02	0.92	0.86	0.99	0.03
4	2,306	56	38-79	0.91	0.85	0.98	0.009	0.90	0.84	0.97	0.005
5 (most deprived)	3,378	56	39-79	0.92	0.86	0.98	0.01	0.92	0.86	0.98	0.01
Age Range	**10,090**	**56**	**39-79**				**<0.001**				**<0.001**
<60	1,861	51	35-71	1.00				1.00			
60-69	3,512	55	37-76	0.94	0.89	0.99	0.02	0.97	0.92	1.03	0.27
70-79	3,531	59	41-84	0.79	0.75	0.84	<0.001	0.85	0.81	0.90	<0.001
80+	1,186	59	41-85	0.76	0.71	0.82	<0.001	0.86	0.80	0.93	<0.001
Sex	**10,090**	**56**	**39-79**				**0.24**				**0.83**
Female	4,508	56	38-78	1.00				1.00			
Male	5,582	56	39-79	0.98	0.94	1.02	0.24	1.00	0.97	1.04	0.83
Histology	**10,090**	**56**	**39-79**				**<0.001**				**<0.001**
NSCLC	7,241	59	43-82	1.00				1.00			
SCLC	1,646	36	26-51	2.19	2.07	2.31	<0.001	1.94	1.83	2.05	<0.001
Other	1,203	62	41-92	0.86	0.80	0.91	<0.001	0.91	0.86	0.97	0.005
Diagnosis year	**10,090**	**56**	**39-79**				**0.0001**				**0.02**
2006	1,682	57	40-83	1.00				1.00			
2007	1,756	56	39-79	1.09	1.02	1.16	0.01	0.90	0.82	0.98	0.01
2008	2,090	55	37-77	1.10	1.03	1.18	0.003	0.87	0.74	1.03	0.11
2009	2,262	56	39-78	1.12	1.05	1.19	0.001	1.07	1.01	1.15	0.04
2010	2,300	55	38-76	1.16	1.09	1.24	<0.001	1.02	0.94	1.10	0.69
Co-morbidity score	**10,090**	**56**	**39-79**				**<0.001**				**<0.001**
0	1,408	57	40-80	1.00				1.00			
1-2	892	62	41-89.5	0.90	0.82	0.98	0.01	1.06	0.99	1.13	0.11
3+	163	56	40-89	0.88	0.75	1.04	0.14	1.07	1.00	1.14	0.05
CCM missing	3,943	55	38-77	1.07	1.01	1.14	0.03	1.15	1.06	1.26	0.001
No HES link	3,684	55	38-76	1.11	1.05	1.18	0.001	1.16	1.06	1.28	0.001
Stage	**10,090**	**56**	**39-79**				**<0.001**				**<0.001**
I	665	71	57-100	1.00				1.00			
II	332	67	54-92	1.14	1.00	1.30	0.05	1.07	0.94	1.22	0.30
III	1,239	56	42-74	1.60	1.46	1.76	<0.001	1.27	1.16	1.41	<0.001
IV	1,454	44	31-61	2.23	2.04	2.45	<0.001	1.69	1.53	1.86	<0.001
Missing/ unknown	6,400	56	38-80	1.46	1.35	1.59	<0.001	1.26	1.14	1.39	<0.001
Performance Status	**10,090**	**56**	**39-79**				**<0.001**				**<0.001**
0	1,305	58	42-76	1.00				1.00			
1-2	2,629	54	38-73	1.07	1.00	1.14	0.05	1.03	0.96	1.10	0.44
3-4	311	42	25-64	1.39	1.23	1.57	<0.001	1.37	1.20	1.55	<0.001
Missing/ unknown	5,845	57	39-82	0.95	0.89	1.00	0.07	0.97	0.89	1.05	0.40
1st treatment	**10,090**	**56**	**39-79**				**<0.001**				**<0.001**
Chemotherapy	4715	48	34-65	1.00				1.00			
Surgery	1856	70	56-94	0.54	0.51	0.57	<0.001	0.69	0.65	0.74	<0.001
Radiotherapy	3519	58	40-85	0.65	0.63	0.68	<0.001	0.80	0.76	0.84	<0.001

[1]Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, stage, PS, 1st treatment

Table 11.12. Odds of receiving any treatment within 62 days of GP referral (for those with FHA within 1 year of referral, diagnosis within 1 year of FHA and treated within 1 year of diagnosis)

	Treatment	Treated within 62 days		Univariable analysis (n=10,090)				Multivariable analysis[1] (n=10,090, R^2=8.75)			
	N	N	%	OR	95% CI		P	OR	95% CI		P
IMD	**10,090**	**6,232**	**61.8**				**0.22**				**0.08**
1 (least deprived)	1,250	806	64.5	1.00				1.00			
2	1,460	902	61.8	0.89	0.76	1.04	0.15	0.89	0.75	1.05	0.16
3	1,696	1,033	60.9	0.86	0.74	1.00	0.05	0.84	0.71	0.98	0.03
4	2,306	1,399	60.7	0.85	0.74	0.98	0.03	0.80	0.69	0.94	0.005
5 (most deprived)	3,378	2,092	61.9	0.90	0.78	1.03	0.11	0.88	0.76	1.01	0.07
Age Range	**10,090**	**6,232**	**61.8**				**<0.001**				**<0.001**
<60	1,861	1,263	67.9	1.00				1.00			
60-69	3,512	2,241	63.8	0.83	0.74	0.94	0.003	0.88	0.78	1.00	0.06
70-79	3,531	2,033	57.6	0.64	0.57	0.72	<0.00	0.70	0.62	0.80	<0.001
80+	1,186	695	58.6	0.67	0.58	0.78	<0.00	0.77	0.65	0.91	0.002
Sex	**10,090**	**6,232**	**61.8**				**0.53**				**0.11**
Female	4,508	2,769	61.4	1.00				1.00			
Male	5,582	3,463	62.0	1.03	0.95	1.11	0.53	1.07	0.98	1.17	0.11
Histology	**10,090**	**6,232**	**61.8**								**<0.001**
NSCLC	7,241	4208	58.1	1.00				1.00			
SCLC	1,646	1393	84.6	3.97	3.44	4.57	<0.001	3.05	2.62	3.55	<0.001
Other	1,203	631	52.5	0.80	0.70	0.90	<0.001	0.87	0.76	0.99	0.03
Co-morbidity score	**10,090**	**6,232**	**61.8**				**<0.001**				**0.0002**
0	1,408	838	59.5	1.00				1.00			
1-2	892	469	52.6	0.75	0.64	0.89	0.001	0.78	0.65	0.94	0.008
3+	163	89	54.6	0.82	0.59	1.13	0.23	0.83	0.59	1.17	0.29
CCM missing	3,943	2,443	62.0	1.11	0.98	1.25	0.11	1.13	0.98	1.30	0.10
No HES link	3,684	2,393	65.0	1.26	1.11	1.43	<0.001	1.07	0.91	1.25	0.44
Diagnosis year	**10,090**	**6,232**	**61.8**								**0.0003**
2006	1,682	983	58.4	1.00				1.00			
2007	1,756	1,032	58.8	1.01	0.88	1.16	0.85	1.01	0.87	1.16	0.90
2008	2,090	1,305	62.4	1.18	1.04	1.35	0.01	1.13	0.99	1.30	0.08
2009	2,262	1,410	62.3	1.18	1.03	1.34	0.01	1.24	1.04	1.50	0.02
2010	2,300	1,502	65.3	1.34	1.18	1.52	<0.001	1.39	1.14	1.69	<0.001
1st treatment	**10,090**	**6,232**	**61.8**								**<0.001**
Chemotherapy	4,715	3,441	73.0	1.00				1.00			
Surgery	1,856	718	38.7	0.23	0.21	0.26	<0.001	0.38	0.34	0.44	<0.001
Radiotherapy	3,519	2,073	58.9	0.53	0.48	0.58	<0.001	0.76	0.69	0.85	<0.001
Stage	**10,090**	**6,232**	**61.8**								**<0.001**
I	665	257	38.7	1.00				1.00			
II	332	147	44.3	1.26	0.97	1.65	0.09	1.07	0.81	1.41	0.64
III	1,239	799	64.5	2.88	2.37	3.50	<0.001	1.56	1.27	1.93	<0.001
IV	1,454	1,136	78.1	5.67	4.65	6.92	<0.001	2.74	2.20	3.41	<0.001
Missing/unknown	6,400	3,893	60.8	2.47	2.09	2.90	<0.001	1.63	1.31	2.03	<0.001
Performance Status	**10,090**	**6,232**	**61.8**								**0.01**
0	1,305	790	60.5	1.000				1.00			
1-2	2,629	1,747	66.5	1.29	1.13	1.48	<0.001	1.07	0.92	1.24	0.40
3-4	311	226	72.7	1.73	1.32	2.28	<0.001	1.31	0.97	1.77	0.08
Missing/ unknown	5,845	3,469	59.4	0.95	0.84	1.08	0.43	0.88	0.73	1.05	0.16

[1]Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, stage, PS, 1st treatment

11.4 Discussion

11.4.1 *Principal Findings*

Socio-economic inequalities in the time intervals from GP referral to FHA, diagnosis, and treatment were found, but socio-economic inequalities were not found in the time intervals from FHA to diagnosis [results not shown], or from diagnosis to treatment. This would suggest that interval inequalities originate from the GP referral to FHA interval. However, a linear trend was not seen. Patients in the middle SEP groups were less likely to receive early FHA, diagnosis or treatment from GP referral, compared to the highest SEP group, but this was not consistently observed for the lowest SEP group.

Generally, those with SCLC, those with poorer PS and those with more advanced stage cancer were more likely to receive FHA, diagnosis and treatment within guidelines. Older patients were less likely to receive first treatment within guidelines. Patients undergoing surgery and radiotherapy as their first treatment had longer time to treatment than those receiving chemotherapy as a first treatment.

11.4.2 *Strengths and weaknesses*

To my knowledge this is the first study to examine factors associated with timely care within UK guidelines for referral, diagnosis and treatment for lung cancer.

In order to accurately determine whether there are inequalities in referral, diagnostic and treatment intervals consistent recording of dates is required. It is likely that FHA and treatment dates are accurately recorded but as a number of different dates can be used for the diagnosis date then, unless there is consistent application of the rules, this could affect calculation of the diagnostic and treatment intervals and thus introduce error. There is no evidence to suggest that the accuracy of recording date of diagnosis is likely to vary by SEP and introduce bias, however.

As the results for time from GP referral to diagnosis and from diagnosis to treatment for those diagnosed in 2010 seemed markedly different to those of earlier years it may be that the different methodology used for determining date of diagnosis in 2010 contributed to these observed differences. It is difficult to say, therefore, whether the likelihood of receiving quicker first treatment in 2010 is a genuine system

improvement or not. However, using the 2006-2009 dataset gave similar results overall.

I examined the interim time interval from FHA to diagnosis. However, the FHA and diagnosis date often appeared to be recorded as the same date [there was a median interval of 0 with 0-0 IQR for 2006-2010 data], which may relate to problems with variability in recording of date of diagnosis in the registry dataset. There did not appear to be socio-economic inequalities within this diagnostic interval but it was difficult to draw any firm conclusions from this analysis when the median time interval in all SEP groups was 0.

It is of course possible that, for those without a GP referral date, the FHA may be an emergency hospital visit where diagnosis is made on that day. Patients who are diagnosed clinically may also have their first clinical appointment date as the date of diagnosis. A UK study also found that the median time from FHA to diagnosis was 0 days [with mean =11.5 days] for lung cancer and was also 0 days in the five other cancer types they looked at, which would suggest that the majority of patients do find out their diagnosis at the FHA (123).

The type of referral route may influence time to diagnosis and treatment. More than half of patients did not have a GP referral date recorded but it was not possible to determine from this data how many of these patients had been referred via a different route and how many may have had a GP referral for which the date was missing. However a large study examining routes to diagnosis found that only 41% of lung cancer patients were referred via their GP and a high proportion of cases (39%) presented as an emergency (255). It was also not possible to determine which patients were urgent GP referrals. However, those who did have a GP date had longer time to treatment than those who did not [a finding similar to that seen in one other study that looked at this for lung cancer (123)], which does suggest that those without a GP date may be presenting as emergency cases and thus receive more urgent investigation and treatment.

In this study I was not able to examine inequalities in the primary care interval [from first patient presentation to the GP until the referral was made], as date of first presentation to GP is not recorded within the registry dataset. I was able to look at

patient delay by using stage at diagnosis and number of DCO cases as proxy measures of patient delay. No evidence for inequalities in delay in patient presentation by SEP was found for the 2006-2010 cohort (chapter 9), in a univariable analysis.

11.4.3 *Interpretation of results and comparison with other studies*

11.4.3.1 *Diagnostic delay*

Two studies from Sweden (73) and Denmark (108), (which have similar healthcare systems to the UK), found socio-economic inequalities in time from referral to diagnosis, with higher SEP patients having more timely diagnosis. I found socio-economic inequalities from GP referral to diagnosis and, within this interval, from GP referral to FHA but not from FHA to diagnosis. A similar result was found in a study which examined socio-economic inequalities in these intervals for pancreatic cancer (29) and a UK study of over 3,000 lung cancer patients also found that socio-economic position was not associated with time from FHA to diagnosis (106). Therefore the evidence does suggest that socio-economic diagnostic inequalities are found in the referral to FHA interval rather than the secondary care FHA to diagnostic interval.

11.4.3.2 *Referral delay*

Patients in England and Wales with suspected cancer should be seen by a specialist within two weeks (24), as an urgent referral. A small 2007 study of 247 UK lung cancer patients found that all patients were referred within this 2 week interval (125). In my study, the median time from GP referral to first hospital appointment was 10 days and 70% of patients were seen in secondary care within the 14 day guideline target, although I did not have details on what type of GP referral these were.

A non-linear trend in socio-economic inequalities in the likelihood of being referred to secondary care within time interval guidelines was found. Those in the middle SEP groups were less likely to receive timely referral than those in the top SEP group, but this was not seen for those in the lowest SEP group.

The Waiting Time Paradox [WTP] suggests that sicker people are referred more quickly and, as they are more ill, actually have shorter survival (179). In our study we found that poorer performance status did result in increased likelihood of earlier referral and diagnosis. This may help to explain why those in the lowest SEP group were not

significantly less likely to receive a timely referral or diagnosis compared to the highest SEP group. Patients with lower SEP had poorer PS [see chapter 9] and so were likely to be in generally poorer health. The results of this 'sicker quicker' effect may, therefore, act to effectively 'cancel out' any system inequalities that might result in longer referral and diagnosis time intervals for lower SEP patients. Those in the bottom SEP group are more likely to receive earlier referral due to being more ill and presenting as an emergency, whereas those at the top are better able to seek urgent referral.

It has been suggested that socio-economic differences in communicating and presenting cancer symptoms to health professionals may result in longer delays for those who are less 'convincing' (111). Lower SEP patients may be less articulate whereas more educated cancer patients are better able to describe symptoms and thus speed up the referral process (104). Differences in health literacy of patients by SEP may contribute to this, where better-educated, more health-literate patients have looked up their symptoms on-line, found out the correct vocabulary and what might be important to mention to the doctor. Doctors may also relate better to wealthier, better educated patients [as they are more similar to themselves in terms of social class and culture] and this may result, possibly unintentionally, in a more rapid investigation process (104).

In a previous study age, sex, ethnicity and marital status did not appear to influence the likelihood of urgent referral for lung cancer (124). We also found that sex was not associated with likelihood of early referral and no clear pattern of referral by age was found.

Patients subsequently diagnosed with earlier-stage cancer and those with good PS had a lower likelihood of being referred within 14 days. It could be argued that it is not appropriate to include stage as a variable in the analysis of time from referral to FHA, as stage is not yet known at this time. A similar argument can also be made for the inclusion of performance status here as, again, this is only ascertained post-FHA. However, stage, PS and co-morbidity score can all be considered as proxy measures for how ill a patient is. Those with earlier stage cancer may not have so many obvious clinical symptoms as patients with later stage cancer. A GP will be prompted to investigate or refer by signs and symptoms of possible cancer. Urgent referral requires

the presence of 'alarm' symptoms that are more likely to be present as the disease advances.

A previous study found that co-morbidity delayed diagnosis in around 20% of lung cancer patients seen by GPs (256). In patients with a number of co-morbidities, lung cancer may not be suspected possibly because symptoms (for example cough, weight loss breathlessness) may be ascribed to a known comorbidity [for example COPD] rather than lung cancer. There is some evidence to suggest that those with lower SEP are likely to have more co-morbidity. One study found that more deprived cancer patients had a 50% higher risk of serious co-morbidity compared to less deprived [high SEP] patients (69). Patients in the lowest SEP group in this study had more co-morbidity and poorer PS than those in the higher SEP groups [table 9.3]. However, no clear-cut pattern was observed in referral or diagnosis time by co-morbidity score in this study, but those with poorer performance status had increased odds of timely FHA and diagnosis.

Both CCM score and PS can be used as proxy measures of general wellbeing/sickness and it is difficult to say how well they capture this. It may be that the number of co-morbidities is not a particularly sensitive measure and PS may be a better marker. However, it may also depend on a patient's prior history as to how a GP interprets their symptoms. If someone regularly visits their GP presenting with multi-morbidities [as measured by CCM score] then the GP may be reluctant to refer that person for yet more testing and the patient may also be reluctant to do so. However if someone with few or no previous comorbidities appears very ill [as measured by performance status] then they may be more likely to be referred for investigation.

11.4.3.3 *Treatment delay*

A previous study that looked at time to treatment targets for lung cancer found that these were not being achieved (101) (125). We found that time to treatment targets were only being met for 43% of patients when measured from diagnosis and 62% when measured from GP referral date [although the type of referral route was not known and could include those not referred under the two-week wait route]. However, some of the reasons for longer delay may be valid. Those who receive curative surgery may undergo a longer period of preliminary investigation with a

greater number of diagnostic and staging procedures, as well as an assessment for fitness for surgery (125). In this study patients who underwent surgery as a first treatment waited a median of 47 days from diagnosis compared to 30 days for chemotherapy and 40 days for radiotherapy. Lower SEP was associated with a longer time to treatment when including both those who did, and did not, receive treatment. This may be because higher SEP patients are more likely to receive treatment. Socio-economic inequalities in receipt of lung cancer treatment were found in my systematic review and meta-analysis (236) and have also been shown for this dataset [see chapter 10]. Late stage and poor performance status were also associated with longer time to treatment. Again, this may be because those with late stage and poorer performance are less likely to receive treatment and thus the time interval appears long as this is censored at the end of the time period rather than treatment being obtained in the interim.

However, when only those patients who received treatment were included in the analysis then SEP was not associated with early treatment from diagnosis. However, in the GP referral to treatment interval, those in the middle SEP groups appeared less likely to receive treatment within the 62 day guidelines, compared to the highest SEP group. Those with later stage cancer and poorer PS were more likely to receive timely treatment within guidelines. Again my previous explanation may be relevant where those in the bottom SEP group are more likely to receive earlier referral and treatment as, due to poorer general health, they are more likely to proceed more speedily through the system and undergo quicker, non-curative treatment such as chemotherapy, whereas those in the top SEP group are more likely to receive curative surgery for which there is a longer interval but they are able to obtain this earlier. Those in the middle groups who are either not so obviously ill or are less able to communicate thus wait the longest for referral and treatment.

11.4.4 *Implications for policy and practice, and further research*

The consistent and accurate recording of GP referral, FHA, diagnosis and first treatment dates by cancer registry staff is important if inequalities in referral, diagnosis and treatment intervals are to be identified. The interval from FHA to diagnosis could not be examined. Due to changes in the way that date of diagnosis was

calculated it was difficult to be sure that any differences seen over time were system changes as a result of the introduction of targets or just due to the change in rules for determining date of diagnosis. Similar studies using other data would be useful to verify this.

Our findings suggest that lower SEP patients are likely to appear more ill [as measured by PS] and the WTP 'sicker quicker' effect may neutralise any patient and system inequalities that might result in longer referral and diagnosis time intervals for lower compared to higher SEP patients, potentially relating to poorer communication and health literacy. Better evidence of inequalities in health literacy by SEP is required. It would also be useful to know more about patient and primary care delay prior to GP referral, and to determine whether socio-economic inequalities are found in these intervals. As around 40% of lung cancer patients present as emergency admissions and there is some evidence that lower SEP patients are more likely to present via this route (77), further investigation into SEP and route to diagnosis is also required.

11.5 Chapter summary

Socio-economic inequalities in the time intervals from GP referral to FHA, diagnosis, and treatment were found, but socio-economic inequalities were not found in the interim intervals from FHA to diagnosis or from diagnosis to treatment. This would suggest that interval inequalities originate from the GP referral to FHA interval. However, a linear trend was not seen. Patients in the middle SEP groups were less likely to receive early FHA, diagnosis or treatment from GP referral, compared to the highest SEP group, but this was not consistently observed for the lowest SEP group. It is possible that the WTP 'sicker quicker' effect may effectively 'cancel out' system inequalities that might result in longer time intervals for lower SEP patients.

The main factors that determined early referral, diagnosis and treatment appeared to be how sick patients appeared, as patients with poor PS and late-stage cancer were more likely to receive early referral and treatment. However, older patients, who were more likely to have poor performance status, were less likely to receive early treatment, indicating possible age-discrimination.

Socio-economic inequalities in lung cancer survival will now be examined in chapter 12.

Chapter 12. Inequalities in survival

Summary

Background

Lung cancer survival is socio-economically patterned and socio-economic inequalities in receipt of treatment have been demonstrated. In England, target waiting times for the referral interval [14 days] and treatment intervals [31 days from diagnosis and 62 days from GP referral] have been set and socio-economic inequalities in the time intervals from GP referral have been found. The contribution of these inequalities to socio-economic inequalities in lung cancer survival is unclear.

Cancer registry [NYCRIS], Hospital Episode Statistics [HES] and lung cancer audit [LUCADA] data-sets were linked in order to investigate the factors that may influence socio-economic inequalities in survival.

Methods

NYCRIS data for 36,477 patients diagnosed between 1999 and 2005 and 28,733 diagnosed between 2006 and 2010 were analysed. Survival time [in weeks] was calculated as the interval from the date of diagnosis to the date of death or to the end of follow up at 31/12/2011 for those still alive. Cox regression models were used to calculate hazard of death, in relation to SEP for those diagnosed in 1999-2005 and 2006-2010. Logistic regression was used to examine the likelihood of still being alive two years after diagnosis for those diagnosed in in 1995-2005 and in 2006-2009.

Results

Those in the lowest SEP group had a significantly higher risk of death. Socio-economic inequalities in survival were no longer found when treatment was included in the model.

Only 15.3% of patients were still alive 2 years after diagnosis but this increased to 70% for those who had surgery. Patients in the lowest SEP group were significantly less likely to still be alive after 2 years, compared to the highest SEP group, in a multivariable analysis adjusted for age, sex, histology, year of diagnosis, GP referral

date, co-morbidity, stage and PS [OR=0.78, 95% CI 0.69 to 0.88, p<0.001]. Adding timely-referral did not substantially change this. However if treatment was included the association no longer remained significant [OR=0.87, 95% CI 0.75 to 1.00, p=0.06] but further addition of timeliness-of-treatment made no difference to the outcome. Patients treated later than the treatment target times had better 2 year survival and lower risk of death than those who received timely treatment.

Conclusions

Socio-economic inequalities in survival are statistically explained by inequalities in receipt of treatment but not by time to treatment in this cohort. However, patients who were treated within the time-to-treatment guideline targets had poorer survival compared to those who had later treatment. Sicker patients had quicker referral through the care pathway and this 'sicker quicker' effect may mask any system inequalities that might otherwise result in longer time intervals in lower SEP patients.

Interventions that address socio-economic inequalities in receipt of treatment are likely to reduce socio-economic inequalities in survival and thus improve survival rates overall.

12.1 Introduction

Survival from lung cancer is socio-economically patterned (135). Socio-economic inequalities in receipt of lung cancer treatment have been demonstrated in a systematic review and meta-analysis (236) conducted as part of this PhD thesis [chapter 7] as well as in the secondary data analysis [chapter 10]. It has been suggested that inequalities in receipt of treatment may at least partially contribute to inequalities in outcome (26) although there is little definitive evidence to support this. Socio-economic inequalities in the time intervals from GP referral to FHA, diagnosis and treatment have also been found [chapter 11] but no linear pattern by SEP emerged. Again it is not known what role inequalities in referral, diagnostic and treatment time may play in survival inequalities.

Cancer registry [NYCRIS], Hospital Episode Statistics [HES] and lung cancer audit [LUCADA] data-sets were linked in order to investigate the factors that may influence socio-economic inequalities in survival for lung cancer patients, specifically examining the influence of socio-economic inequalities in receipt of treatment, and in timely GP referral and treatment, taking into account age, sex, histology, year of diagnosis, co-morbidity, stage and performance status.

12.2 Methods

12.2.1 *Data*

For details of data sources and variables see chapter 8, sections 8.2 and 8.4. The following variables were included in multivariable analyses: SEP, age, sex, histology, year of diagnosis, co-morbidity, stage, PS, type of treatment [no treatment, surgery, surgery + chemotherapy or radiotherapy, chemotherapy, chemotherapy and radiotherapy, radiotherapy], timely GP referral [FHA within 14 days of GP referral, FHA>14 days from GP referral, or no GP referral date], timely first treatment [first treatment within 31 days of diagnosis, or first treatment >31 days from diagnosis].

12.2.2 *Analysis*

Kaplan Meier graphs were used to examine univariable influences on all-cause mortality. Cox regression models were used to calculate hazard ratios [HRs] and 95% CIs for all-cause mortality in relation to SEP, in multivariable models for those

diagnosed in 1999-2005 and 2006-2010. As date of diagnosis was determined in a different way in 2010 from previous years then analysis of the 2006-2009 dataset [n=22,967] and of the 2006-2009 dataset with stage recorded [n=5233] was also carried out. Nelson-Aalen plots were used to check the proportional hazard assumptions for the potential explanatory variables in each model.

Logistic regression was used to examine the likelihood of still being alive two years after diagnosis, by SEP, in the 1995-2005 cohort and in the 2006-2009 dataset. Interactions between SEP and histology, and SEP and type of treatment received, were explored. The R^2 statistic was examined to determine the amount of variance in survival explained by each model.

12.3 Results

12.3.1 *Descriptive statistics*

Similar results were found in the 1999-2005 cohort compared to those for 2006-2010 and 2006-2009 and so to avoid repetition the 1999-2005 tables are found in appendix D.

Figs 12.1 – 12.13 show univariable Kaplan-Meier survival curves for patients diagnosed between 2006 and 2010, plotting proportion of patients surviving [y axis] over time [x axis]. Results for 1999-2005 and for 2006-2009 all showed similar patterns [results not shown].

Median survival was 24 weeks in the least deprived SEP group and 21 in the most deprived [table 12.1]. Although survival inequalities by SEP were found [Fig 12.1] these were less pronounced than for survival inequalities by age [Fig 12.2] and sex [Fig 12.3].

Survival inequalities by tumour type were observed [Fig 12.4] with the best survival found for the small number of patients who have a non-standard histology code [other-specified histology], with 41% of these still alive at 2 years compared to 25.3% for adenocarcinoma and 24% for those diagnosed with squamous cell carcinoma in the 2006-2009 cohort. Only 8.3% of those diagnosed with SCLC were still alive at 2 years [table 12.4].

Figure 12.1. Kaplan-Meier survival curve: SEP

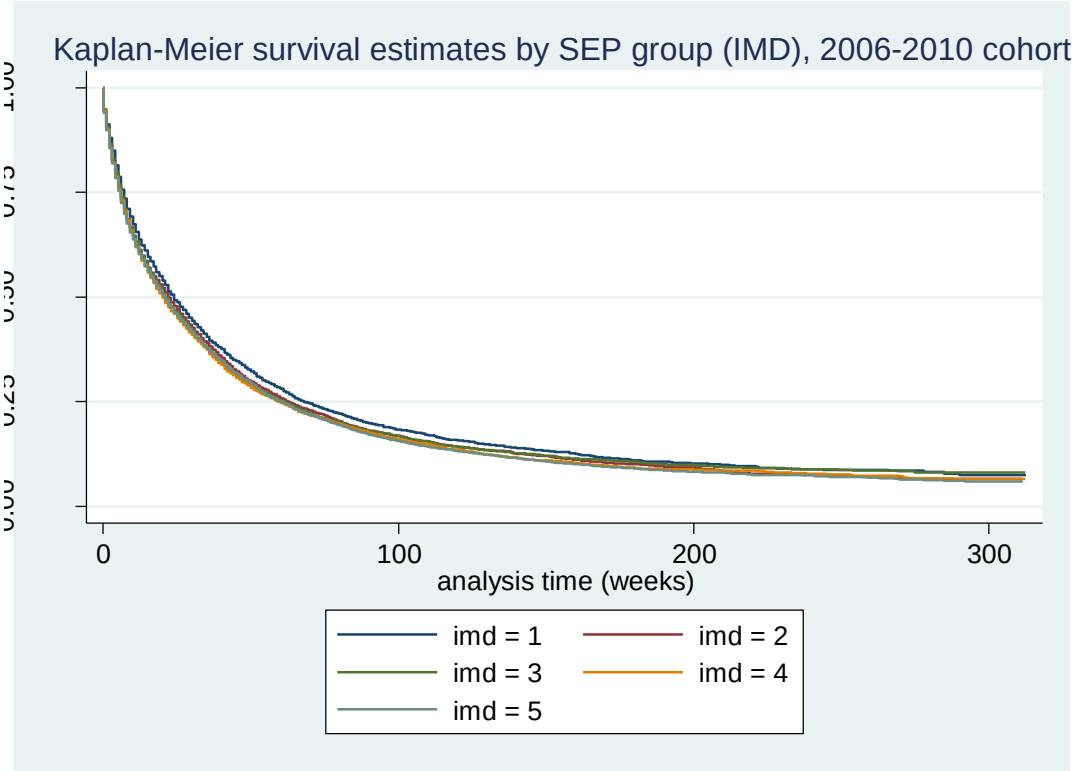


Figure 12.2. Kaplan-Meier survival curve: age

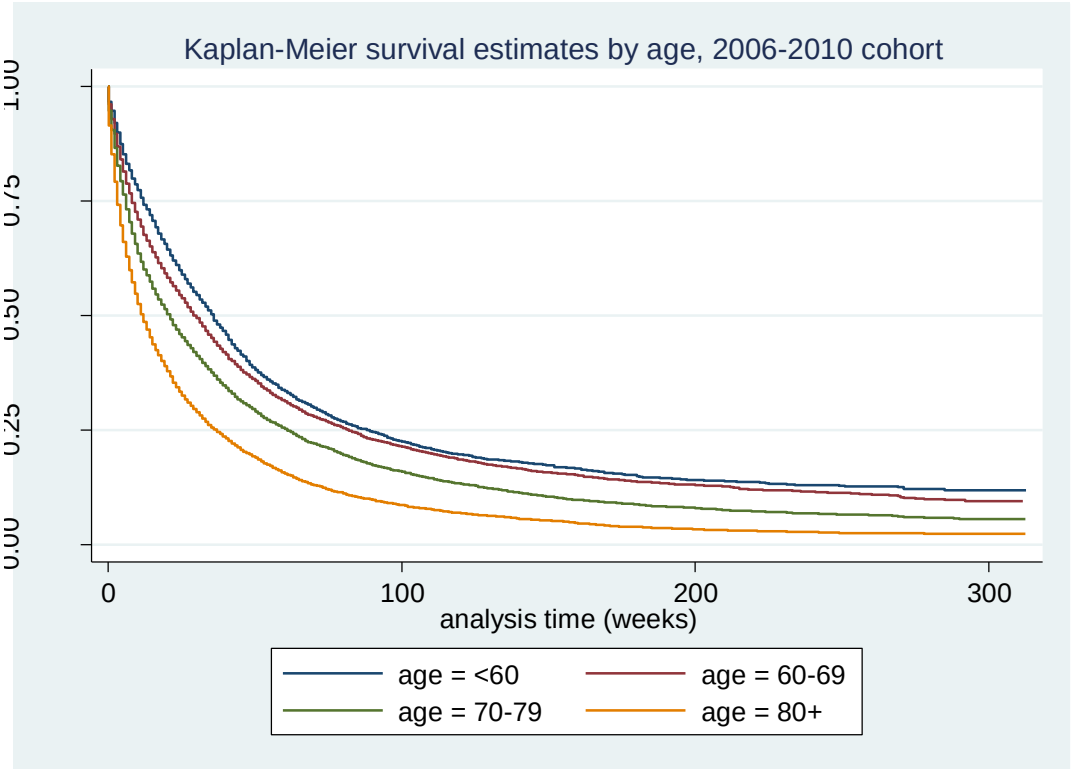


Figure 12.3. Kaplan-Meier survival curve: sex

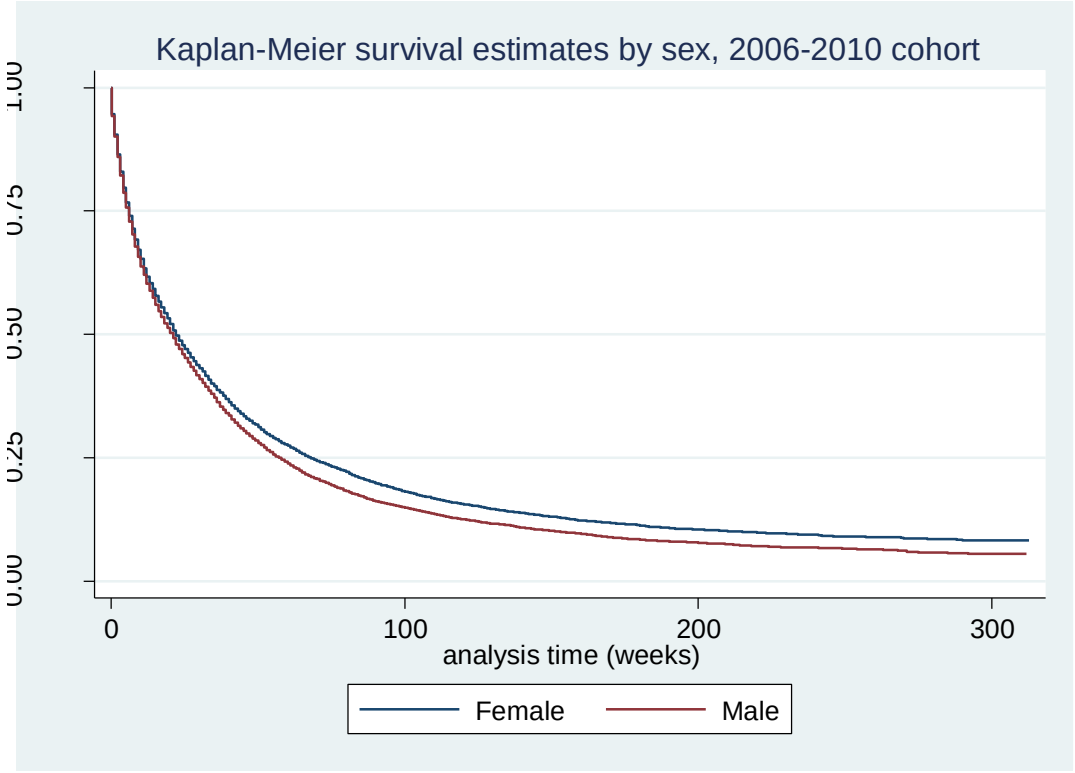
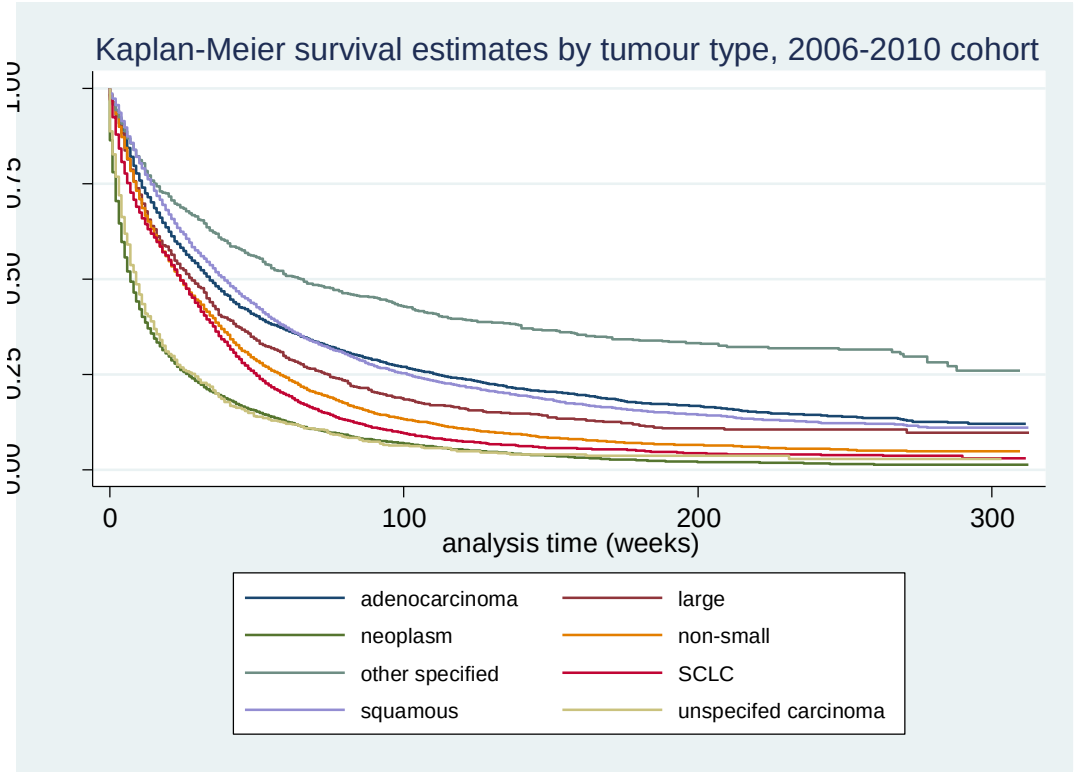


Figure 12.4. Kaplan-Meier survival curve: tumour type



Survival also varied markedly by performance status [Fig 12.5] with a median survival of 64 weeks for those with good PS [PS=0] compared to 34 weeks with PS=1-2 and 8 weeks for those with poor PS [PS=3-4] [table 12.1]. However, survival differences by number of co-morbidities was less pronounced [Fig 12.6] with only small median survival differences found between those who had no co-morbidities recorded [23 weeks], 1-2 co-morbidities [20 weeks] and 3 or more co-morbidities [18 weeks] [table 12.1].

Patients who underwent surgery had the best survival [Fig 12.7]. Interestingly survival one year after diagnosis was better for those who surgery plus chemotherapy/radiotherapy compared to surgery alone, but this reversed shortly after, with those having surgery alone having the best overall survival [73.0% at 2 years compared to 64.4% in the multiple treatment group for the 2006-2009 data-set] [table 12.4].

Fig 12.8 shows survival by type of, and time to, first treatment. Those who had surgery later than 31 days from diagnosis had the best survival although after four years those who had surgery within the 31 day target had similar survival. Patients who had radiotherapy as a 1st treatment within the 31 day target from diagnosis had similar survival to those who had no treatment, after one year. Those who had first treatment within 31 days had poorer survival [median survival 32 weeks] compared to those who had first treatment later than 31 days from diagnosis [median survival 55 weeks] [Fig 12.9].

Figs 12.10-12.12 show survival by receipt of and time to, surgery, chemotherapy and radiotherapy respectively and again it can be seen that those who had treatment later than the 31 day target from diagnosis had better survival than those who had timely treatment. For chemotherapy and radiotherapy the best survival was found for those who had treatment more than 62 days after diagnosis but these graphs do not take into account whether any other treatment was also received.

Fig 12.13 shows survival by stage. Patients with early stage cancer had better survival than those with later stage cancer.

Figure 12.5. Kaplan-Meier survival curve: PS

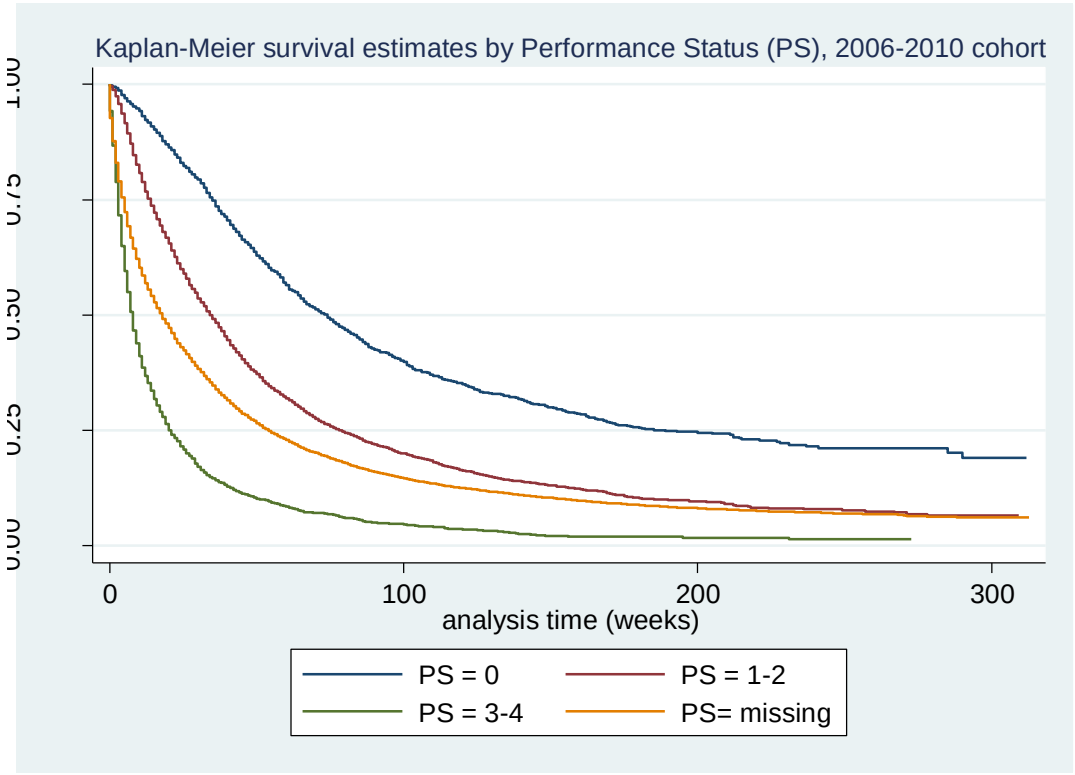


Figure 12.6. Kaplan-Meier survival curve: co-morbidity

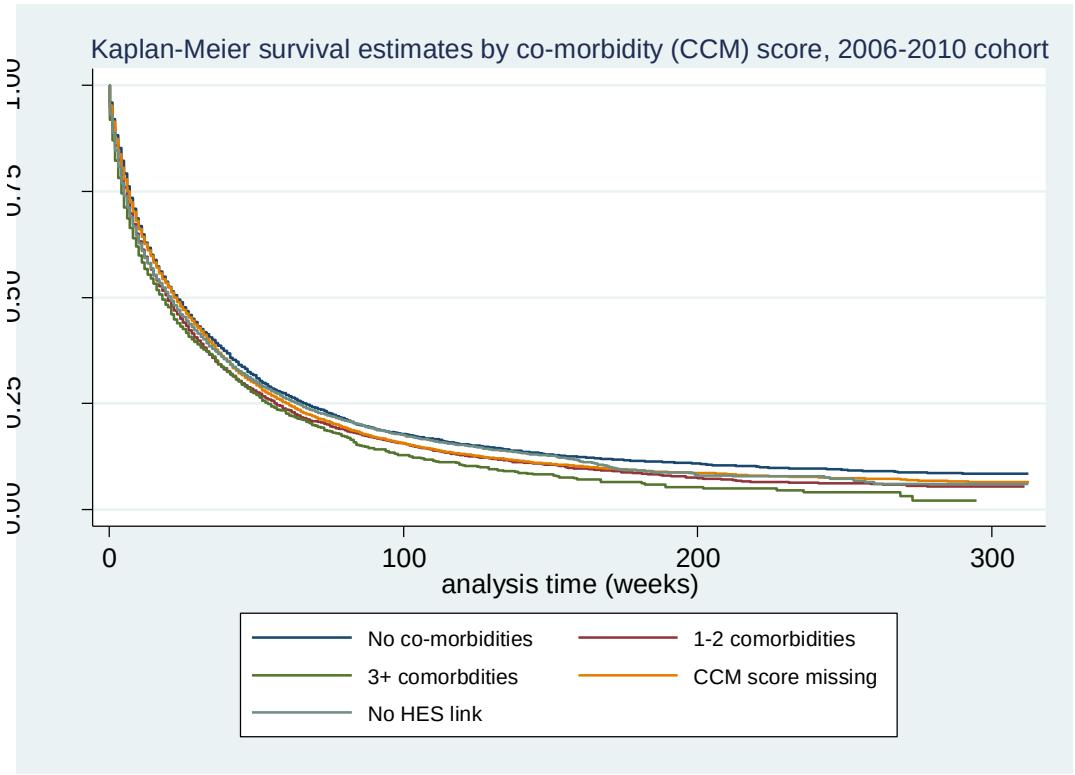


Figure 12.7. Kaplan-Meier survival curve: treatment type

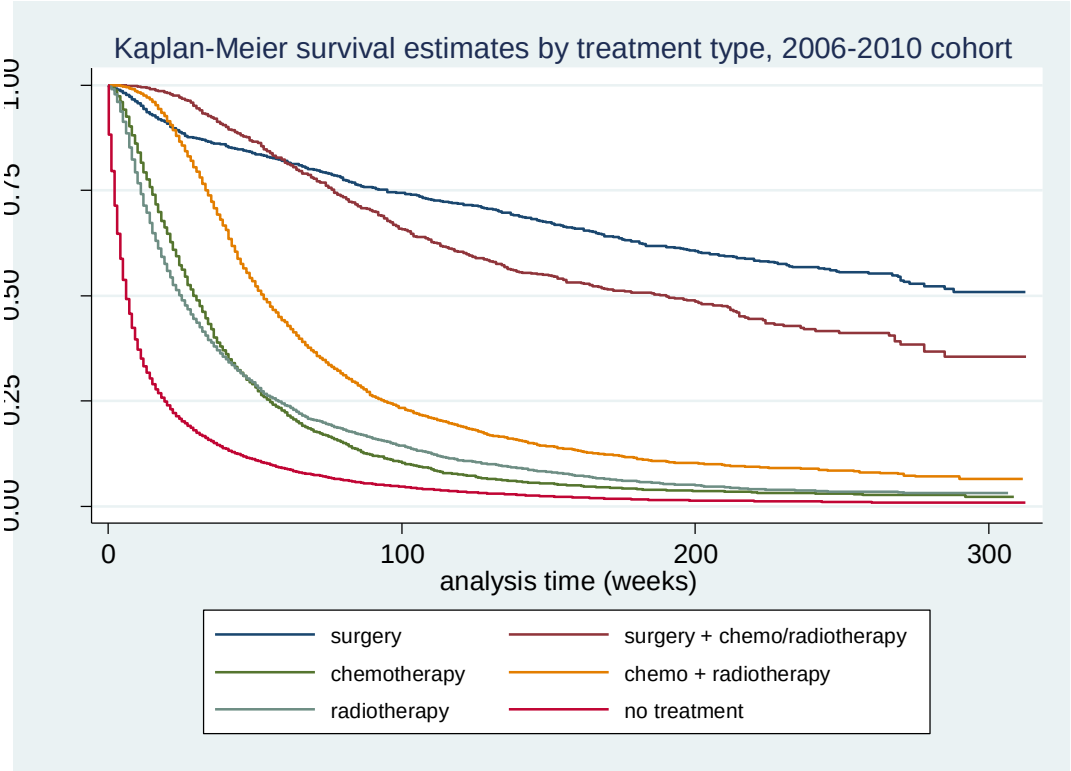


Figure 12.8. Kaplan-Meier survival curve: time to, and type of, treatment

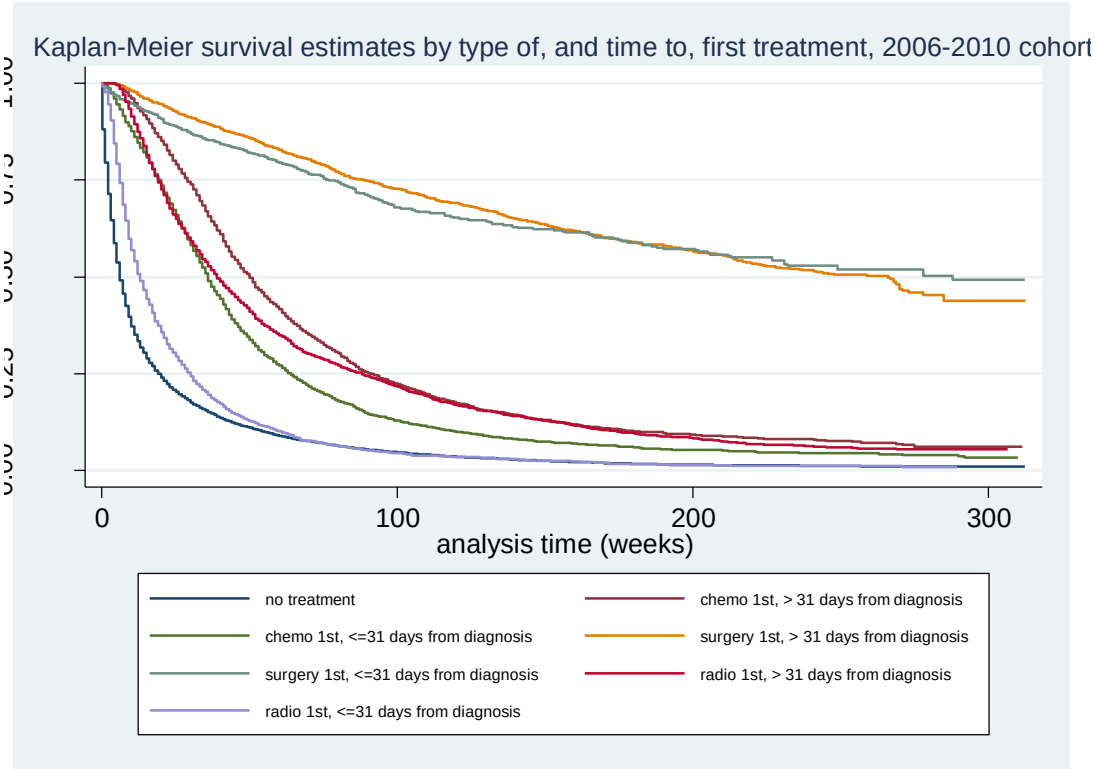


Figure 12.9. Kaplan-Meier survival curve: time to first treatment

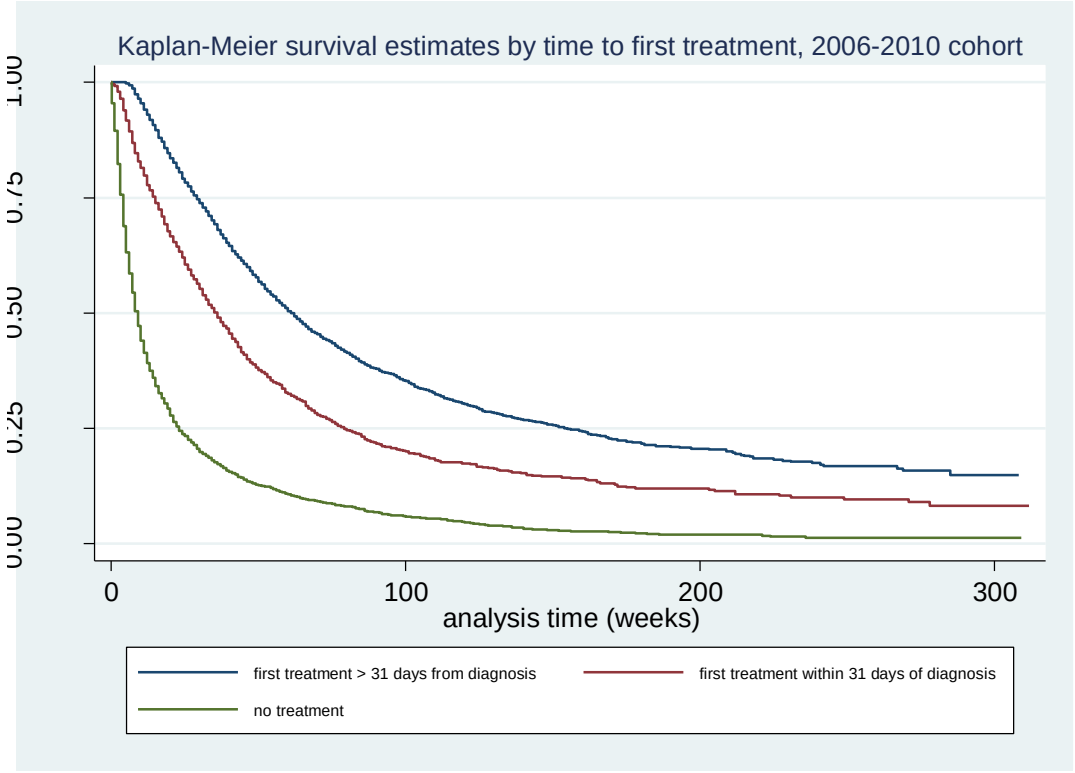


Figure 12.10. Kaplan-Meier survival curve: timely surgery

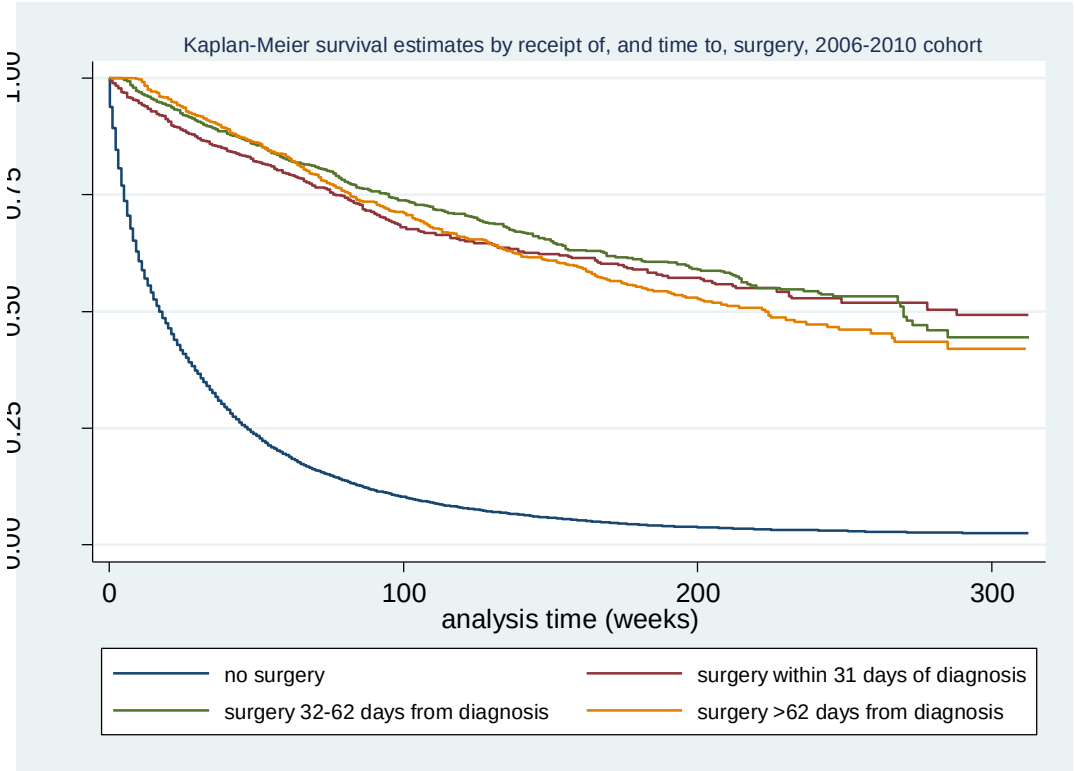


Figure 12.11. Kaplan-Meier survival curve: timely chemotherapy

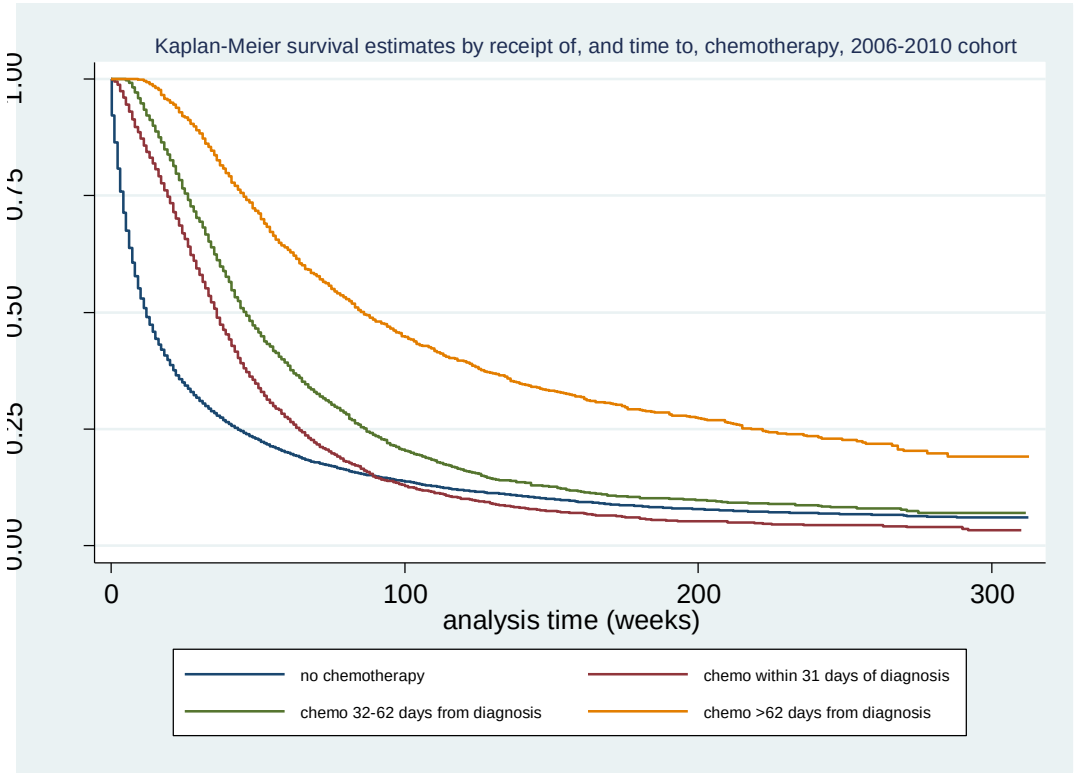


Figure 12.12. Kaplan-Meier survival curve: timely radiotherapy

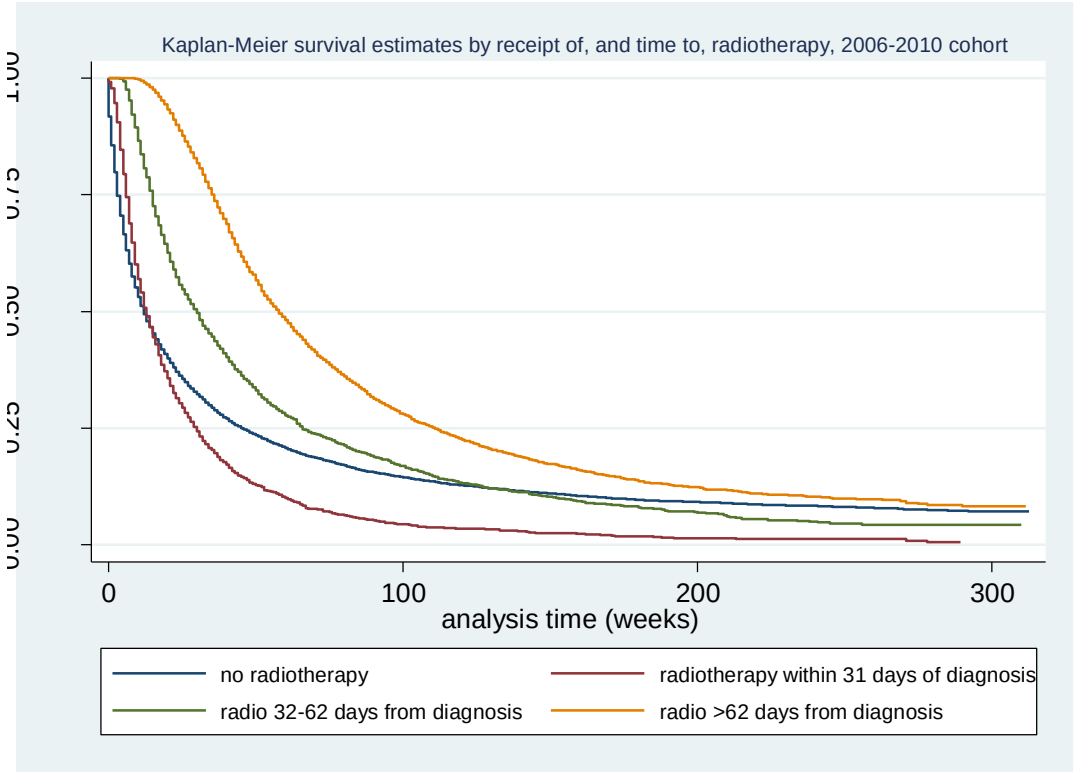
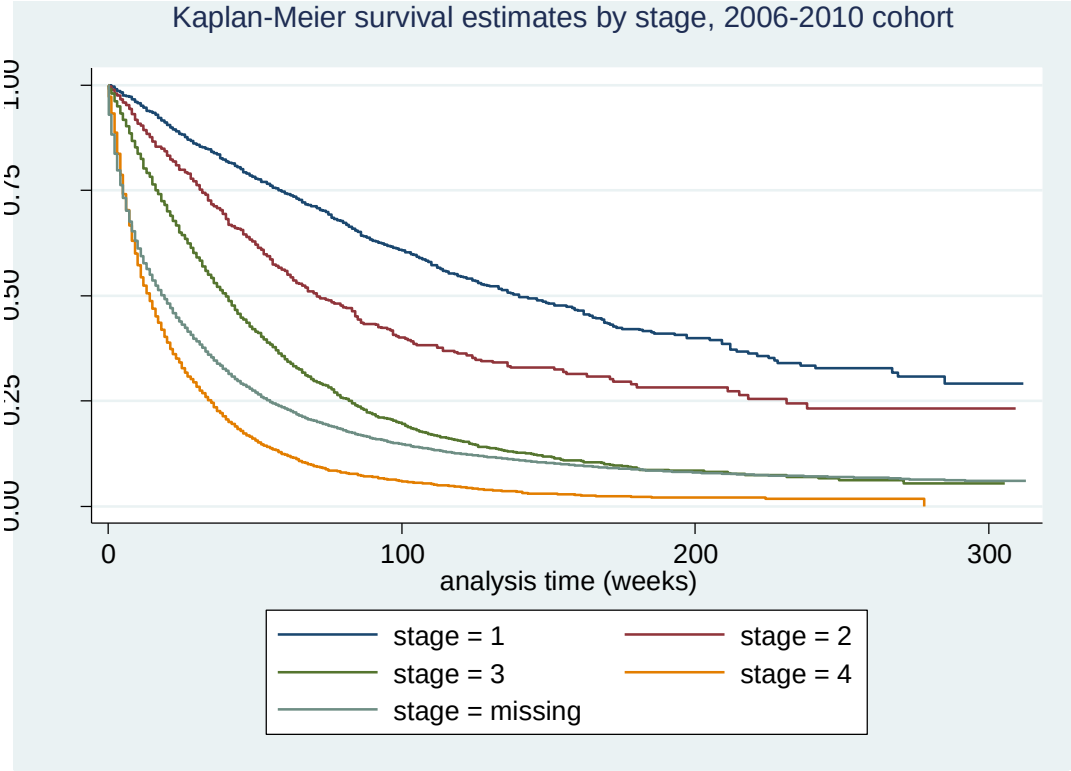


Figure 12.13. Kaplan-Meier survival curve: stage



12.3.2 *Risk (HR) of all-cause mortality*

12.3.2.1 *Descriptive analysis: 2006-2010 cohort*

Median survival in this cohort was 21 weeks from diagnosis [IQR 6-59.3] [table 12.1].

Socio-economic inequalities in survival were found in the unadjusted analyses. In the univariable Cox regression analyses those in the most deprived group had a significantly higher risk [HR] of death than those in the most affluent [HR=1.10, 95% CI 1.05 to 1.14, p<0.001] [table 12.2]. Those in the oldest age group, men, those with no treatment, later stage cancer and poorer performance status all had significantly higher risk of death.

Patients who had their first treatment greater than 31 days after diagnosis had better survival compared to those who had treatment within the 31 day guideline [median survival of 55 weeks compared to 32], as did those who had a FHA greater than 14 days from GP referral compared to those who had referral within guidelines [median survival of 37 compared to 30 weeks] [table 12.1]. Those in the no treatment group had the poorest survival.

Table 12.1. Median survival (weeks), by selected patient, tumour and system factors for the cohort diagnosed between 2006 and 2010, and for the 2006-2010 subset with stage (DCO cases excluded)

Variable	2006-2010 Cohort	Median survival (weeks)		2006-2010 Cohort with stage	Median survival (weeks)	
	N	N	IQR	N	N	IQR
Deprivation quintile	**28,733**	**21**	**6-59.3**	**7769**	**30**	**10-68.1**
1 (least deprived)	3389	24	7-64	931	34	11-76
2	4178	22	6-60.3	1118	33	10-71
3	4948	21	6-59	1300	30	10-68.6
4	6710	20	6-58	1831	28	9-64.1
5 (most deprived)	9608	21	6-58.6	2589	29	9-67.7
Age group	**28,733**	**21**	**6-59.3**	**7769**	**30**	**10-68.1**
<60	3682	36	12-78	1041	41	16-77
60-69	7595	30	8-72	2189	39	12-80
70-79	10248	21	6-59	2843	28	9-67
80+	7208	12	3-37	1696	18	6-51
Sex	**28,733**	**21**	**6-59.3**	**7769**	**30**	**10-68.1**
Female	13254	22	6-63	3559	31	11-72
Male	15479	21	6-56	4210	29	9-66
Histology	**28,733**	**21**	**6-59.3**	**7769**	**30**	**10-68.1**
NSCLC	15123	32	11-74.7	5116	38	14-78
SCLC	3495	24	7-50	582	29	8-54
Other	10115	9	2-36	2071	14	4-49
Year of Diagnosis	**28,733**	**21**	**6-59.3**	**7769**	**30**	**10-68.1**
2006	5533	20	6-57	671	36	12-85
2007	5712	21	6-60	866	34.5	11-88
2008	5851	21	6-58	1556	27	10-71
2009	5871	23	6-67	2140	30	9-85
2010	5766	22	6-58	2536	29	8-60.7
Co-morbidity Score	**28,733**	**21**	**6-59.3**	**7769**	**30**	**10-68.1**
0	4010	23	7-65	995	30	11-75
1-2	3531	20	6-57	857	28	9-75
3+	934	18	4-54	226	21	7-61
CCM missing	10175	22	7-61	1977	32	11-79
No HES link	10083	21	5-58.6	3714	30	9-64.6
Timely GP referral	**28,733**	**21**	**6-59.3**	**7769**	**30**	**10-68.1**
No GP referral date	13281	12	3-42	2418	19	6-57
FHA<=14 days	11019	30	9-66	4087	33	11-71
FHA>14 days	4433	37	13-78	1264	44	17-79.3
Stage	**28,733**	**21**	**6-59.3**	**7769**	**30**	**10-68.1**
I	1186	88	56-139.6	1186	88	56-139.6
II	552	61.5	32-99.6	552	61.5	32-99.6
III	2273	40	17-72.1	2273	40	17-72.1
IV	3758	14	5-35	3758	14	5-35
missing	20964	19	5-55	--	--	--
Performance Status	**28,733**	**21**	**6-59.3**	**7769**	**30**	**10-68.1**
0	1842	64	35-108	1493	65	36-107.6
1-2	4865	34	14-69.9	3870	35	14-70
3-4	2178	8	3-21	1763	8	3-20
Missing	19848	18	5-54	643	22	7-64.6

Table 12.1 (cont). Median survival (weeks), by selected patient, tumour and system factors for the cohort diagnosed between 2006 and 2010, and for the 2006-2010 subset with stage (DCO cases excluded)

Variable	2006-2010 Cohort	Median survival (weeks)		2006-2010 Cohort with stage	Median survival (weeks)	
	N	N	IQR	N	N	IQR
Type of treatment	**28,733**	**21**	**6-59.3**	**7769**	**30**	**10-68.1**
No treatment	13291	6	2-19	2815	9	4-23
Surgery	1833	120.4	66-194.3	579	103.1	64.7-153.5
Surgery + chemotherapy/ radiotherapy	1061	103	64.3-166.4	422	96.5	64.1-150.7
Chemotherapy	3404	30	15-55	1051	32	16-56
Chemotherapy+radiotherapy	4117	53	34-84	1329	55	35-82
Radiotherapy	5027	25	11-57	1573	28	12-63
Timely 1st treatment	**28,733**	**21**	**6-59.3**	**7769**	**30**	**10-68.1**
>31 days from diagnosis	8887	55	27-108.6	2979	58	29-104.6
<=31 days from diagnosis	6555	32	13-65	1975	36	15-67.3

12.3.2.2 *Multivariable regression analysis: 2006-2010 cohort*

In the multivariable analysis including age and sex a survival gradient by SEP was seen [HR=1.13, 95% CI 1.09 to 1.18, p<0.001]. This remained when histology, year of diagnosis, co-morbidity and timely GP referral were taken into account [HR=1.13, 95% CI 1.09 to 1.18, p<0.001] [table 12.2] and on addition of stage and PS [HR=1.11, 95% CI 1.07 to 1.16, p<0.001] [table 12.2] but not once receipt of treatment was included in the model [HR=1.02, 95% CI 0.98 to 1.06, p=0.36] [table 12.2]. Addition of timeliness of treatment to the model did not change the findings [HR=1.03, 95% CI 0.98 to 1.07, p=0.22].

12.3.2.3 *2006-2009 cohort*

An identical pattern of results was seen for the 2006-2009 dataset [results not shown].

Table 12.2. Likelihood of mortality (hazard ratio of death), by selected patient, tumour and system factors for those diagnosed between 2006 and 2010 (DCO cases excluded)

Variable	Unadjusted (n=28,733)				Adjusted – IMD, age, sex, histology, year, CCM, timely GP referral (n=28,733)			
	HR	95% CI		P	HR	95% CI		P
Deprivation quintile				**0.0002**				**<0.001**
1 (least deprived)	1.00				1.00			
2	1.06	1.01	1.11	0.02	1.07	1.02	1.12	0.009
3	1.06	1.01	1.11	0.01	1.06	1.01	1.11	0.02
4	1.09	1.05	1.14	<0.001	1.12	1.07	1.17	<0.001
5 (most deprived)	1.10	1.05	1.14	<0.001	1.13	1.09	1.18	<0.001
Age group				**<0.001**				**<0.001**
<60	1.00				1.00			
60-69	1.09	1.04	1.14	<0.001	1.10	1.05	1.14	<0.001
70-79	1.33	1.28	1.39	<0.001	1.29	1.24	1.35	<0.001
80+	1.83	1.75	1.91	<0.001	1.62	1.55	1.69	<0.001
Sex				**<0.001**				**<0.001**
Female	1.00				1.00			
Male	1.10	1.07	1.12	<0.001	1.14	1.12	1.17	<0.001
Histology				**<0.001**				**<0.001**
NSCLC	1.00				1.00			
SCLC	1.39	1.34	1.44	<0.001	1.43	1.37	1.48	<0.001
Other	1.76	1.71	1.81	<0.001	1.52	1.48	1.57	<0.001
Year of Diagnosis				**<0.001**				**0.28**
2006	1.00				1.00			
2007	0.97	0.94	1.01	0.15	0.98	0.94	1.02	0.25
2008	0.97	0.93	1.01	0.14	0.98	0.94	1.02	0.37
2009	0.90	0.86	0.93	<0.001	0.95	0.91	1.00	0.03
2010	0.91	0.88	0.95	<0.001	0.95	0.91	1.00	0.07
Co-morbidity score								**<0.001**
0	1.00				1.00			
1-2	1.12	1.06	1.17	<0.001	1.01	0.96	1.06	0.81
3+	1.20	1.11	1.29	<0.001	1.02	0.94	1.09	0.70
CCM missing	1.06	1.02	1.10	0.002	1.13	1.08	1.17	<0.001
No HES link	1.06	1.02	1.10	0.004	1.07	1.03	1.12	0.002
Timely GP referral				**<0.001**				**<0.001**
No GP ref date	1.00				1.00			
FHA<=14 days	0.68	0.66	0.70	<0.001	0.73	0.71	0.76	<0.001
FHA>14 days	0.60	0.57	0.62	<0.001	0.63	0.61	0.66	<0.001
Stage				**<0.001**				
I	1.00							
II	1.54	1.35	1.76	<0.001				
III	2.61	2.38	2.87	<0.001				
IV	4.86	4.45	5.31	<0.001				
Missing	3.63	3.34	3.95	<0.001				
Performance Status				**<0.001**				
0	1.00							
1-2	1.73	1.63	1.85	<0.001				
3-4	4.05	3.77	4.35	<0.001				
Missing	2.34	2.21	2.49	<0.001				

Table 12.2 (cont). Likelihood of mortality (HR of death), by selected patient, tumour and system factors for those diagnosed between 2006 and 2010 (DCO cases excluded)

Variable	Adjusted – IMD, age, sex, histology, year, CCM, timely GP referral, stage, PS (n=28,733)				Adjusted – IMD, age, sex, histology, year, CCM, timely GP referral, stage, PS, treatment type (n=28,733)			
	HR	95% CI		P	HR	95% CI		P
Deprivation quintile				**<0.001**				**0.51**
1 (least deprived)	1.00				1.00			
2	1.07	1.02	1.12	0.007	1.04	0.99	1.10	0.08
3	1.05	1.00	1.10	0.05	1.03	0.98	1.08	0.23
4	1.10	1.05	1.15	<0.001	1.02	0.98	1.07	0.29
5 (most deprived)	1.11	1.07	1.16	<0.001	1.02	0.98	1.06	0.36
Age group				**<0.001**				**<0.001**
<60	1.00				1.00			
60-69	1.09	1.05	1.14	<0.001	0.96	0.92	1.00	0.07
70-79	1.28	1.22	1.33	<0.001	0.91	0.87	0.95	<0.001
80+	1.57	1.50	1.65	<0.001	0.85	0.81	0.89	<0.001
Sex				**<0.001**				**<0.001**
Female	1.00				1.00			
Male	1.15	1.12	1.18	<0.001	1.14	1.11	1.17	<0.001
Histology				**<0.001**				**<0.001**
NSCLC	1.00				1.00			
SCLC	1.36	1.31	1.42	<0.001	1.52	1.46	1.59	0.00
Other	1.44	1.40	1.49	<0.001	0.99	0.96	1.03	0.70
Year of Diagnosis				**0.61**				**<0.001**
2006	1.00				1.00			
2007	0.98	0.94	1.02	0.31	0.99	0.95	1.03	0.63
2008	0.98	0.94	1.02	0.33	0.98	0.95	1.02	0.43
2009	0.97	0.93	1.02	0.22	1.14	1.09	1.19	<0.001
2010	0.96	0.91	1.01	0.12	1.15	1.09	1.21	<0.001
Co-morbidity score				**<0.001**				**<0.001**
0	1.00				1.00			
1-2	1.01	0.96	1.06	0.77	0.92	0.87	0.96	<0.001
3+	1.01	0.94	1.09	0.75	0.89	0.82	0.96	0.002
CCM missing	1.12	1.07	1.16	<0.001	1.11	1.07	1.16	<0.001
No HES link	1.07	1.02	1.12	0.003	0.92	0.88	0.96	<0.001
Timely GP referral				**<0.001**				**<0.001**
No GP ref date	1.00				1.00			
FHA<=14 days	0.75	0.73	0.77	<0.001	0.84	0.82	0.87	<0.001
FHA>14 days	0.66	0.63	0.68	<0.001	0.75	0.72	0.78	<0.001
Stage				**<0.001**				**<0.001**
I	1.00				1.00			
II	1.61	1.41	1.84	<0.001	1.42	1.24	1.62	<0.001
III	2.68	2.44	2.95	<0.001	2.05	1.87	2.25	<0.001
IV	4.65	4.25	5.08	<0.001	3.29	3.01	3.60	<0.001
Missing	2.82	2.58	3.09	<0.001	2.26	2.06	2.48	<0.001
Performance Status				**<0.001**				**<0.001**
0	1.00				1.00			
1-2	1.39	1.30	1.49	<0.001	1.12	1.05	1.20	<0.001
3-4	2.49	2.31	2.68	<0.001	1.55	1.44	1.67	<0.001
Missing	1.71	1.60	1.84	<0.001	1.34	1.25	1.44	<0.001
Type of treatment								**<0.001**
No treatment					1.00			
Surgery					0.09	0.08	0.10	<0.001
Surgery +chemo/radiotherapy					0.12	0.11	0.13	<0.001
Chemotherapy					0.40	0.38	0.42	<0.001
Chemo+radiotherapy					0.25	0.24	0.26	<0.001
Radiotherapy					0.50	0.48	0.51	<0.001

Table 12.3. Likelihood of mortality (hazard ratio of death), by selected patient, tumour and system factors for the subset diagnosed between 2006 and 2010 with stage recorded (DCO cases excluded)

Variable	Adjusted – IMD, age, sex, histology, year, CCM, timely GP referral (n=28,733)				Adjusted – IMD, age, sex, histology, year, CCM, timely GP referral, stage (n=28,733)			
	HR	95% CI		P	HR	95% CI		P
Deprivation quintile				**0.0004**				**0.002**
1 (least deprived)	1.00				1.00			
2	1.06	0.96	1.16	0.27	1.06	0.96	1.17	0.22
3	1.07	0.97	1.17	0.18	1.08	0.98	1.18	0.13
4	1.17	1.07	1.27	0.001	1.16	1.06	1.27	0.001
5 (most deprived)	1.17	1.07	1.27	<0.001	1.16	1.06	1.26	0.001
Age group				**<0.001**				**<0.001**
<60	1.00				1.00			
60-69	1.02	0.94	1.11	0.65	1.06	0.98	1.16	0.14
70-79	1.21	1.12	1.32	0.00	1.34	1.24	1.45	<0.001
80+	1.49	1.37	1.63	0.00	1.70	1.55	1.85	<0.001
Sex				**<0.001**				**<0.001**
Female	1.00				1.00			
Male	1.13	1.07	1.19	<0.001	1.13	1.07	1.19	<0.001
Histology				**<0.001**				**<0.001**
NSCLC	1.00				1.00			
SCLC	1.46	1.33	1.60	<0.001	1.18	1.08	1.30	<0.001
Other	1.48	1.39	1.57	<0.001	1.55	1.46	1.65	<0.001
Year of Diagnosis				**0.16**				**0.96**
2006	1.00				1.00			
2007	1.01	0.91	1.12	0.90	0.98	0.88	1.10	0.77
2008	1.08	0.98	1.19	0.12	0.98	0.89	1.08	0.71
2009	1.10	0.98	1.23	0.09	1.01	0.90	1.13	0.86
2010	1.13	1.01	1.27	0.03	1.02	0.91	1.15	0.76
Co-morbidity score				**0.02**				**0.03**
0	1.00				1.00			
1-2	0.95	0.86	1.06	0.36	1.02	0.92	1.13	0.72
3+	1.07	0.92	1.25	0.40	1.18	1.01	1.38	0.04
CCM missing	1.11	1.01	1.21	0.03	1.04	0.95	1.14	0.43
No HES link	0.97	0.89	1.05	0.45	0.94	0.86	1.02	0.15
Timely GP referral				**<0.001**				**<0.001**
No GP referral date	1.00				1.00			
FHA<=14 days	0.78	0.74	0.83	<0.001	0.77	0.73	0.81	<0.001
FHA>14 days	0.66	0.61	0.71	<0.001	0.70	0.65	0.75	<0.001
Stage								**<0.001**
I					1.00			
II					1.73	1.52	1.98	<0.001
III					3.16	2.88	3.48	<0.001
IV					6.54	5.96	7.16	<0.001

Table 12.3 (cont). Likelihood of mortality (HR of death), by selected patient, tumour and system factors for those diagnosed between 2006 and 2010 with stage recorded (DCO cases excluded)

variable	Adjusted – IMD, age, sex, histology, year, CCM, timely GP referral ,stage, PS (n=28,733)				Adjusted – IMD, age, sex, histology, year, CCM, stage, PS, timely GP referral, treatment type (n=28,733)			
	HR	**95% CI**		**P**	**HR**	**95% CI**		**P**
Deprivation quintile				**0.18**				**0.45**
1 (least deprived)	1.00				1.00			
2	1.05	0.95	1.15	0.37	1.07	0.97	1.18	0.16
3	1.01	0.92	1.11	0.76	1.03	0.93	1.13	0.61
4	1.10	1.01	1.20	0.04	1.07	0.98	1.16	0.16
5 (most deprived)	1.06	0.97	1.15	0.21	1.02	0.94	1.11	0.60
Age group				**<0.001**				**<0.001**
<60	1.00				1.00			
60-69	1.00	0.92	1.09	0.99	0.95	0.87	1.03	0.20
70-79	1.13	1.04	1.22	0.005	0.86	0.79	0.94	0.001
80+	1.28	1.17	1.40	<0.001	0.81	0.73	0.89	<0.001
Sex				**<0.001**				**<0.001**
Female	1.00				1.00			
Male	1.15	1.10	1.21	<0.001	1.15	1.09	1.21	<0.001
Histology				**<0.001**				**<0.001**
NSCLC	1.00				1.00			
SCLC	1.12	1.02	1.23	0.02	1.42	1.29	1.57	<0.001
Other	1.25	1.18	1.33	<0.001	0.95	0.89	1.02	0.15
Year of Diagnosis				**0.65**				**0.0009**
2006	1.00				1.00			
2007	0.96	0.87	1.07	0.49	0.98	0.88	1.09	0.65
2008	0.95	0.86	1.04	0.26	0.98	0.89	1.08	0.66
2009	1.00	0.89	1.12	0.99	1.17	1.04	1.30	0.008
2010	1.01	0.90	1.14	0.86	1.18	1.05	1.33	0.005
Co-morbidity score				**0.05**				**<0.001**
0	1.00				1.00			
1-2	0.95	0.86	1.05	0.34	0.90	0.81	0.99	0.03
3+	1.05	0.90	1.23	0.55	0.91	0.78	1.06	0.23
CCM missing	1.06	0.97	1.17	0.18	1.04	0.95	1.14	0.43
No HES link	0.93	0.85	1.01	0.09	0.83	0.76	0.91	<0.001
Timely GP referral				**<0.001**				**<0.001**
No GP referral date	1.00				1.00			
FHA<=14 days	0.80	0.76	0.85	<0.001	0.87	0.82	0.92	<0.001
FHA>14 days	0.74	0.69	0.80	<0.001	0.81	0.75	0.87	<0.001
Stage				**<0.001**				**<0.001**
I	1.00				1.00			
II	1.66	1.45	1.90	<0.001	1.54	1.34	1.76	<0.001
III	2.96	2.69	3.25	<0.001	2.44	2.21	2.70	<0.001
IV	5.88	5.36	6.45	<0.001	4.52	4.10	4.98	<0.001
Performance Status				**<0.001**				**<0.001**
0	1.00				1.00			
1-2	1.51	1.40	1.63	<0.001	1.22	1.13	1.32	<0.001
3-4	3.45	3.15	3.77	<0.001	2.08	1.89	2.28	<0.001
Missing	1.94	1.75	2.16	<0.001	1.53	1.37	1.70	<0.001
Type of treatment								**<0.001**
No treatment					1.00			
Surgery					0.18	0.15	0.21	<0.001
Surgery +chemo/radiotherapy					0.17	0.14	0.20	<0.001
Chemotherapy					0.42	0.38	0.46	<0.001
Chemo+radiotherapy					0.28	0.26	0.31	<0.001
Radiotherapy					0.59	0.54	0.63	<0.001

12.3.2.4 *2006-2010 subset with stage recorded*

Median survival in the staged cohort was better than for the full 2006-2010 cohort [median of 30 compared to 21 weeks].

In the subset with stage recorded [n=7769] socio-economic inequalities in survival were found in a univariable analysis [OR=1.13, 95% CI 1.04 to 1.22, p=0.005] and in multivariable analyses when age and sex, histology, year of diagnosis, co-morbidity, timely GP referral and stage were included in the analysis [OR=1.16, 95% CI 1.06 to 1.26, p=0.001], but not when PS was added to the model [OR=1.06, 95% CI 0.97 to 1.15, p=0.21] [table 12.3] and not when receipt of treatment was included [OR=1.02, 95% CI 0.94 to 1.11, p=0.60]. Further addition of timely treatment did not alter this.

12.3.2.5 *2006-2009 subset with stage recorded*

In the 2006-2009 subset with stage recorded [n=5233] an identical pattern of results to the 2006-2010 cohort with stage recorded was again found [results not shown].

12.3.3 *Two year survival: 2006-2009 data-set*

12.3.3.1 *Descriptive analysis*

In the 2006 to 2009 data-set [n=22,967], 15.3% of patients [3513] were still alive two years after diagnosis [table 12.4]. In the unadjusted analysis those in the lowest SEP group were significantly less likely to still be alive after 2 years, compared to the highest SEP group [OR=0.79, 95% CI 0.70 to 0.89, p<0.001] [table 12.5].

Likelihood of two-year survival was better for patients with high SEP, younger patients, women, those diagnosed with NSCLC, those with no co-morbidity, early stage patients, those with good PS, those referred by their GP and those receiving treatment. Patients who received surgery between 32-62 days after diagnosis had the greatest likelihood of two-year survival. For chemotherapy and radiotherapy optimal survival was found for those who had treatment more than 62 days after diagnosis [table 12.4].

12.3.3.2 *Multivariable regression analysis*

In a multivariable analysis adjusted for age, sex, histology, year of diagnosis, timely GP referral and co-morbidity, inequalities in survival by SEP were observed, with a

reduced likelihood of 2 year survival in the lowest compared to the highest SEP group [OR=0.74, 95% CI 0.66 to 0.84, p<0.001] [table 12.5]. The amount of survival variation explained by the model was poor [R^2=5.77]. Adding stage and PS improved this [R^2=12.31] but did not substantially change the SEP OR [OR=0.77, 95% CI 0.66 to 0.88, p<0.001]. However if treatment type [surgery, surgery plus chemotherapy/radiotherapy, chemotherapy, chemotherapy plus radiotherapy, radiotherapy] was included in the analysis the association no longer remained significant [OR=0.87, 95% CI 0.75 to 1.00, p=0.06]. Receipt of treatment also made the greatest contribution to explaining survival variance in the model [R^2=27.97]. Further addition of timeliness of treatment made no difference to the outcome [OR=0.87, 95% CI 0.75 to 1.00, p=0.05]. No significant interactions between SEP and type of treatment [or SEP and histology] were found.

Patients treated later than the referral and treatment target times had better 2-year survival than those who received timely treatment.

Similar results were found for the 1999-2005 cohort. Socio-economic inequalities in survival were found in a univariable analysis [OR=0.81, 95% CI 0.73 to 0.90, p=0.006] and remained when adjusted for age, sex, year of diagnosis, co-morbidity and timely referral [OR=0.84, 95% CI 0.76 to 0.94, p<0.001, R^2=5.80] but were no longer found when treatment was added to the model [OR=1.06, 95% CI 0.94 to 1.20, p=0.38 R^2=24.60] [appendix D, table D5]. Stage and PS were not available for these years.

12.3.3.3 *2006-2009 subset with stage recorded*

In the 2006 to 2009 subset with stage recorded [n=5233] socio-economic inequalities in survival were found in a multivariable analysis including age, sex, histology, year of diagnosis, co-morbidity and timely GP referral, with those in the most deprived group having a significantly lower likelihood of 2-year survival than those in the most affluent [OR=0.76, 95% CI 0.61 to 0.76, p=0.02], but with poor explanation of survival variance using this model [R^2=3.72].

However, the association was no longer significant when stage was added [OR=0.79, 95% CI 0.61 to 0.82, p=0.07], with a large increase in R^2 to 24.39. The addition of PS further attenuated the OR (OR=0.90, 95% CI 0.70 to 1.17, p=0.45) [table 12.6] as did

the addition of treatment [OR=1.03, 95% CI 0.78 to 1.36, p=0.85]. Stage and receipt of treatment contributed most to the explanation for survival variance in the model but PS and treatment had the greatest influence on likelihood of survival by SEP.

Table 12.4 Survival at 2 years: descriptive data and univariable ORs for 2006-2009 cohort

Variable	Cohort	Survival at 2 years		Unadjusted (n=22,967)			
	N	N	%	OR	95% CI		P
Deprivation quintile	**22,967**	**3,513**	**15.3**				**0.004**
1 (least deprived)	2,698	474	17.6	1.00			
2	3,303	520	15.7	0.88	0.76	1.00	0.06
3	3,827	586	15.3	0.85	0.74	0.97	0.02
4	5,387	815	15.1	0.84	0.74	0.95	0.005
5 (most deprived)	7,752	1,118	14.4	0.79	0.70	0.89	<0.001
Age group	**22,967**	**3,513**	**15.3**				**<0.001**
<60	3,041	651	21.4	1.00			
60-69	6,016	1,199	19.9	0.91	0.82	1.02	0.10
70-79	8,219	1,210	14.7	0.63	0.57	0.70	<0.001
80+	5,691	453	8.0	0.32	0.28	0.36	<0.001
Sex	**22,967**	**3,513**	**15.3**				**<0.001**
Female	10,510	1,770	16.8	1.00			
Male	12,457	1,743	14.0	0.80	0.75	0.86	<0.001
Histology	**22,967**	**3,513**	**15.3**				**<0.001**
NSCLC	12,152	2,463	20.3	1.00			
SCLC	2,829	236	8.3	0.36	0.31	0.41	<0.001
Other	7,986	814	10.2	0.45	0.41	0.49	<0.001
Histology (alternative)	**22,967**	**3,513**	**15.3**				**<0.001**
Probable NSCLC	13053	2835	21.7	1.00			
SCLC	2,829	236	8.3	0.33	0.29	0.38	<0.001
Unspecified	7085	442	6.2	0.24	0.22	0.27	<0.001
Year of Diagnosis	**22,967**	**3,513**	**15.3**				**<0.001**
2006	5,533	783	14.2	1.00			
2007	5,712	844	14.8	1.05	0.95	1.17	0.35
2008	5,851	861	14.7	1.05	0.94	1.16	0.39
2009	5,871	1,025	17.5	1.28	1.16	1.42	<0.001
Co-morbidity	**22,967**	**3,513**	**15.3**				**0.0006**
0	3,597	601	16.7	1.00			
1-2	3,125	453	14.5	0.85	0.74	0.97	0.01
3+	766	89	11.6	0.66	0.52	0.83	<0.001
CCM missing	10,133	1,509	14.9	0.87	0.79	0.97	0.009
No HES link	5,346	861	16.1	0.96	0.85	1.07	0.45
Stage	**22,967**	**3,513**	**15.3**				**<0.001**
I	864	504	58.3	1.00			
II	332	128	38.6	0.45	0.35	0.58	<0.001
III	1,587	276	17.4	0.15	0.12	0.18	<0.001
IV	2,450	139	5.7	0.04	0.03	0.05	<0.001
missing	17,734	2,466	13.9	0.12	0.10	0.13	<0.001
Performance Status	**22,967**	**3,513**	**15.3**				**<0.001**
0	1,298	481	37.1	1.00			
1-2	3,414	635	18.6	0.39	0.34	0.45	<0.001
3-4	1,415	65	4.6	0.08	0.06	0.11	<0.001
Missing	16,840	2,332	13.9	0.27	0.24	0.31	<0.001
Timely treatment	**22,967**	**3,513**	**15.3**				**<0.001**
>31 days from diagnosis	7,443	2,346	31.5	1.00			
<=31 days from diagnosis	4,849	708	14.6	0.37	0.34	0.41	<0.001
No treatment	10,675	459	4.3	0.10	0.09	0.11	<0.001

Table 12.4 (cont). Survival at 2 years: descriptive data and univariable ORs for 2006-2009 cohort

Variable	Cohort	Survival at 2 years		Unadjusted (n=22,967)			
	N	N	%	OR	95% CI		P
Timely GP referral	22,967	3,513	15.3				**<0.001**
No GP referral date	11,014	1,254	11.4	1.00			
FHA<=14 days	8,284	1,456	17.6	1.66	1.53	1.80	<0.001
FHA>14 days	3,669	803	21.9	2.18	1.98	2.40	<0.001
Tumour type	**22,967**	**3,513**	**15.3**				**<0.001**
Adenocarcinoma	3,409	861	25.3	1.00			
Squamous	4,141	992	24.0	0.93	0.84	1.04	0.19
Large	640	116	18.1	0.66	0.53	0.81	<0.001
Non-small	3,962	494	12.5	0.42	0.37	0.48	<0.001
Other specified	901	372	41.3	2.08	1.78	2.43	<0.001
Small	2,829	236	8.3	0.27	0.23	0.31	<0.001
Unspecified carcinoma	442	26	5.9	0.18	0.12	0.28	<0.001
Neoplasm	6,643	416	6.3	0.20	0.17	0.22	<0.001
Surgery Y/N	**22,967**	**3,513**	**15.3**				**<0.001**
No surgery	20731	1951	9.4	1.00			
Surgery	2236	1562	69.9	22.31	20.15	24.69	<0.001
Chemotherapy Y/N	**22,967**	**3,513**	**15.3**				**<0.001**
No chemotherapy	16340	2104	12.9	1.00			
Chemotherapy	6627	1409	21.3	1.83	1.70	1.97	<0.001
Radiotherapy Y/N	**22,967**	**3,513**	**15.3**				**<0.001**
No radiotherapy	15320	2108	13.8	1.00			
Radiotherapy	7647	1405	18.4	1.41	1.31	1.52	<0.001
Type of 1st treatment	**22,967**	**3,513**	**15.3**				**<0.001**
No treatment	10,675	459	4.3	1.00			
Surgery 1st	2193	1534	70.0	51.81	45.46	59.04	<0.001
Chemotherapy 1st	5490	892	16.3	4.32	3.84	4.86	<0.001
Radiotherapy 1st	4609	628	13.6	3.51	3.10	3.98	<0.001
Type of treatment	**22,967**	**3,513**	**15.3**				**<0.001**
No treatment	10,675	459	4.3	1.00			
Surgery	1,427	1,041	73.0	60.02	51.68	69.71	<0.001
Surgery +chemo/ radiotherapy	809	521	64.4	40.26	33.91	47.80	<0.001
Chemotherapy	2,759	267	9.7	2.38	2.04	2.79	<0.001
Chemotherapy+radiotherapy	3,236	701	21.7	6.15	5.43	6.98	<0.001
Radiotherapy	4,061	524	12.9	3.30	2.89	3.76	<0.001
Surgery	**22,967**	**3,513**	**15.3**				**<0.001**
No surgery	20,731	1,951	9.41	1.00			
Surgery <31 days from diagnosis	515	333	64.7	17.61	14.61	21.22	<0.001
Surgery 32-62 days from diagnosis	943	686	72.8	25.69	22.10	29.87	<0.001
Surgery > 62 days from diagnosis	778	543	69.8	22.24	18.95	26.10	<0.001
Chemotherapy	**22,967**	**3,513**	**15.3**				**<0.001**
No chemotherapy	16,340	2,104	12.9	1.00			
Chemotherapy <31 days from diagnosis	2,782	324	11.7	0.89	0.79	1.01	0.07
Chemotherapy 32-62 days from diagnosis	2,267	420	18.5	1.54	1.37	1.73	<0.001
Chemotherapy >62 days from diagnosis	1,578	665	42.1	4.93	4.42	5.50	<0.001

Table 12.4 (cont). Survival at 2 years: descriptive data and univariable ORs for 2006-2009 cohort

Variable	Cohort	Survival at 2 years		Unadjusted (n=22,967)			
	N	N	%	OR	95% CI		P
Radiotherapy	**22,967**	**3,513**	**15.3**				**<0.001**
No radiotherapy	15,320	2,108	13.8	1.00			
Radiotherapy <31 days from diagnosis	1,649	62	3.8	0.24	0.19	0.32	<0.001
Radiotherapy 32-62 days from diagnosis	1,871	268	14.3	1.05	0.91	1.20	0.51
Radiotherapy > 62 days from diagnosis	4,127	1,075	26.1	2.21	2.03	2.40	<0.001
Timely 1st Treatment	**22,967**	**3,513**	**15.3**				**<0.001**
No treatment	10,675	459	4.3	1.00			
Chemotherapy 1st >31 days from diagnosis	2,775	577	20.8	5.84	5.13	6.66	<0.001
Chemotherapy 1st <31 days from diagnosis	2,715	315	11.6	2.92	2.51	3.39	<0.001
Surgery 1st >31 days from diagnosis	1,678	1,201	71.6	56.04	48.65	64.55	<0.001
Surgery 1st <31 days from diagnosis	515	333	64.7	40.72	33.23	49.91	<0.001
Radiotherapy 1st >31 days from diagnosis	2,990	568	19.0	5.22	4.58	5.95	<0.001
Radiotherapy 1st <31 days from diagnosis	1,619	60	3.7	0.86	0.65	1.13	0.27

Table 12.5. Likelihood of still being alive 2 years after diagnosis, by selected patient, tumour and system factors for those diagnosed between 2006 and 2009 (DCO cases excluded)

Variable	Adjusted – IMD, age, sex, histology, year, CCM, timely referral (n=22,967, R^2=5.77)				Adjusted – IMD, age, sex, histology, year, CCM, timely referral, stage, PS (n=22,967, R^2=12.31)			
	OR	95% CI		P	OR	95% CI		P
Deprivation quintile				**<0.001**				**0.002**
1 (least deprived)	1.00				1.00			
2	0.87	0.76	1.00	0.05	0.87	0.76	1.01	0.07
3	0.86	0.75	0.98	0.03	0.87	0.75	1.00	0.05
4	0.80	0.70	0.91	0.001	0.83	0.72	0.95	0.005
5 (most deprived)	0.74	0.66	0.84	<0.001	0.77	0.68	0.88	<0.001
Age group				**<0.001**				**<0.001**
<60	1.00				1.00			
60-69	0.93	0.83	1.03	0.17	0.92	0.82	1.03	0.14
70-79	0.65	0.58	0.73	<0.001	0.64	0.57	0.71	<0.001
80+	0.35	0.31	0.41	<0.001	0.34	0.30	0.39	<0.001
Sex				**<0.001**				**<0.001**
Female	1.00				1.00			
Male	0.74	0.69	0.80	<0.001	0.73	0.67	0.79	<0.001
Histology				**<0.001**				**<0.001**
NSCLC	1.00				1.00			
SCLC	0.34	0.30	0.40	<0.001	0.36	0.31	0.42	<0.001
Other	0.60	0.55	0.66	<0.001	0.64	0.58	0.71	<0.001
Year of Diagnosis				**0.08**				**0.20**
2006	1.00				1.00			
2007	1.06	0.95	1.18	0.30	1.05	0.94	1.18	0.35
2008	1.06	0.95	1.19	0.27	1.08	0.96	1.21	0.18
2009	1.19	1.04	1.36	0.01	1.16	1.01	1.33	0.04
Co-morbidity score				**0.007**				**0.01**
0	1.00				1.00			
1-2	0.95	0.83	1.09	0.50	0.94	0.81	1.08	0.38
3+	0.84	0.66	1.07	0.16	0.79	0.61	1.03	0.08
CCM missing	0.82	0.74	0.92	<0.001	0.83	0.74	0.93	0.001
No HES link	0.94	0.82	1.07	0.32	0.97	0.85	1.11	0.66
Timely GP referral				**<0.001**				**<0.001**
No GP referral	1.00				1.00			
FHA<=14 days	1.44	1.32	1.58	<0.001	1.40	1.28	1.53	<0.001
FHA>14 days	1.98	1.79	2.19	<0.001	1.80	1.62	2.01	<0.001
Stage								**<0.001**
I					1.00			
II					0.38	0.29	0.50	<0.001
III					0.13	0.11	0.16	<0.001
IV					0.04	0.03	0.05	<0.001
missing					0.17	0.14	0.20	<0.001
Performance Status								**<0.001**
0					1.00			
1-2					0.55	0.47	0.65	<0.001
3-4					0.18	0.14	0.24	<0.001
Missing					0.45	0.38	0.54	<0.001

Table 12.5 (b). Likelihood of still being alive 2 years after diagnosis, by selected patient, tumour and system factors for those diagnosed between 2006 and 2009 (DCO cases excluded)

variable	Adjusted – IMD, age, sex, histology, year, CCM, timely referral, stage, PS, treatment type (n=22,967, R^2=27.97)				Adjusted – IMD, age, sex, histology, year, CCM, timely referral, stage, PS, treatment type, timely 1st treatment (n=22,967, R^2=28.74)			
	OR	95% CI		P	OR	95% CI		P
Deprivation quintile				**0.34**				**0.34**
1 (least deprived)	1.00				1.00			
2	0.88	0.75	1.04	0.13	0.88	0.75	1.04	0.14
3	0.90	0.77	1.06	0.22	0.90	0.76	1.05	0.18
4	0.94	0.81	1.09	0.41	0.94	0.81	1.09	0.39
5 (most deprived)	0.87	0.75	1.00	0.06	0.87	0.75	1.00	0.05
Age group				**0.11**				**0.04**
<60	1.00				1.00			
60-69	1.04	0.91	1.18	0.60	1.02	0.89	1.16	0.80
70-79	0.94	0.82	1.07	0.33	0.90	0.79	1.03	0.12
80+	0.88	0.74	1.03	0.12	0.84	0.71	1.00	0.05
Sex				**<0.001**				**<0.001**
Female	1.00				1.00			
Male	0.72	0.66	0.79	<0.001	0.71	0.65	0.78	<0.001
Histology				**<0.001**				**<0.001**
NSCLC	1.00				1.00			
SCLC	0.46	0.40	0.54	<0.001	0.57	0.49	0.67	<0.001
Other	1.28	1.14	1.44	<0.001	1.33	1.18	1.50	<0.001
Year of Diagnosis				**0.009**				**0.009**
2006	1.00				1.00			
2007	1.02	0.90	1.15	0.77	1.00	0.88	1.13	0.95
2008	1.08	0.95	1.23	0.22	1.02	0.90	1.16	0.75
2009	0.83	0.71	0.98	0.03	0.80	0.68	0.93	0.005
Co-morbidity score				**<0.001**				**<0.001**
0	1.00				1.00			
1-2	1.10	0.93	1.29	0.25	1.10	0.93	1.29	0.25
3+	0.96	0.72	1.28	0.79	0.96	0.72	1.29	0.81
CCM missing	0.84	0.73	0.95	0.006	0.83	0.73	0.95	0.006
No HES link	1.37	1.17	1.60	<0.001	1.38	1.18	1.61	<0.001
Timely GP referral				**<0.001**				**<0.001**
No GP referral date	1.00				1.00			
FHA<=14 days	1.16	1.05	1.29	0.004	1.14	1.03	1.26	0.02
FHA>14 days	1.40	1.25	1.58	<0.001	1.36	1.20	1.53	<0.001
Stage				**<0.001**				**<0.001**
I	1.00				1.00			
II	0.48	0.35	0.68	<0.001	0.49	0.35	0.69	<0.001
III	0.29	0.23	0.36	<0.001	0.30	0.24	0.38	<0.001
IV	0.12	0.09	0.15	<0.001	0.13	0.10	0.17	<0.001
Missing	0.31	0.25	0.38	<0.001	0.33	0.27	0.41	<0.001
Performance Status				**0.001**				
0	1.00				1.00			
1-2	0.88	0.73	1.05	0.16	0.89	0.74	1.07	0.20
3-4	0.59	0.43	0.81	0.001	0.61	0.44	0.83	0.002
Missing	0.73	0.60	0.90	0.002	0.72	0.59	0.88	0.002

Table 12.5 (b, cont). Likelihood of still being alive 2 years after diagnosis, by selected patient, tumour and system factors for those diagnosed between 2006 and 2009 (DCO cases excluded)

variable	Adjusted – IMD, age, sex, histology, year, CCM, stage, PS, timely referral, treatment type (n=22,967, R^2=27.97)				Adjusted – IMD, age, sex, histology, year, CCM, stage, PS, timely referral, treatment type, timely 1st treatment (n=22,967, R^2=28.74)			
	OR	**95% CI**		**P**	**OR**	**95% CI**		**P**
Type of treatment				**<0.001**				**<0.001**
No treatment	1.00				1.00			
Surgery	49.77	41.93	59.07	<0.001	60.95	51.12	72.66	<0.001
Surgery +chemo/ radiotherapy	33.00	26.99	40.34	<0.001	40.47	32.96	49.69	<0.001
Chemotherapy	3.25	2.71	3.91	<0.001	4.19	3.47	5.05	<0.001
Chemotherapy+radiotherapy	7.83	6.65	9.22	<0.001	10.03	8.48	11.86	<0.001
Radiotherapy	3.34	2.89	3.87	<0.001	4.12	3.55	4.78	<0.001
Timely 1st treatment								**<0.001**
>31 days from diagnosis					1.00			
<31 days from diagnosis					0.50	0.45	0.56	<0.001

Table 12.6. Likelihood of still being alive 2 years after diagnosis, by selected patient, tumour and system factors for those diagnosed between 2006 and 2009 (DCO cases excluded) with stage recorded

Variable	Adjusted – IMD, age, sex, histology, year, CCM, timely GP referral (n=5233, R^2=3.72)				Adjusted – IMD, age, sex, histology, year, CCM, timely GP referral, stage (n=5233, R^2=24.39)				Adjusted – IMD, age, sex, histology, year, CCM, timely GP referral, stage, PS (n=5233, R^2=26.59)			
	OR	**95% CI**		**P**	**OR**	**95% CI**		**P**	**OR**	**95% CI**		**P**
Deprivation quintile				**0.02**				**0.07**				**0.22**
1 (least deprived)	1.00				1.00				1.00			
2	0.92	0.71	1.20	0.54	0.93	0.69	1.25	0.62	0.97	0.72	1.31	0.83
3	0.92	0.72	1.19	0.53	0.92	0.69	1.23	0.56	1.00	0.75	1.34	0.99
4	0.72	0.56	0.91	0.007	0.71	0.54	0.93	0.01	0.77	0.58	1.02	0.06
5 (most deprived)	0.76	0.61	0.96	0.02	0.79	0.61	1.02	0.07	0.90	0.70	1.17	0.45
Age group				**<0.001**				**<0.001**				**<0.001**
<60	1.00				1.00				1.00			
60-69	1.06	0.86	1.31	0.60	0.94	0.74	1.20	0.63	1.03	0.81	1.32	0.79
70-79	0.79	0.64	0.97	0.03	0.60	0.47	0.77	<0.001	0.75	0.59	0.96	0.02
80+	0.53	0.41	0.68	<0.001	0.35	0.26	0.47	<0.001	0.49	0.36	0.67	<0.001
Sex				**<0.001**				**<0.001**				**<0.001**
Female	1.00				1.00				1.00			
Male	0.75	0.65	0.86	<0.001	0.72	0.61	0.84	<0.001	0.70	0.59	0.82	<0.001
Histology				**<0.001**				**<0.001**				**<0.001**
NSCLC	1.00				1.00				1.00			
SCLC	0.32	0.22	0.47	<0.001	0.49	0.32	0.75	0.001	0.49	0.32	0.76	0.001
Other	0.65	0.54	0.78	<0.001	0.61	0.50	0.76	<0.001	0.80	0.64	1.00	0.05
Year of Diagnosis				**0.70**				**0.29**				**0.93**
2006	1.00				1.00				1.00			
2007	1.03	0.80	1.33	0.83	1.04	0.78	1.39	0.78	1.07	0.80	1.43	0.66
2008	0.91	0.72	1.15	0.42	1.04	0.80	1.37	0.75	1.09	0.83	1.44	0.52
2009	0.95	0.72	1.25	0.70	1.09	0.80	1.49	0.58	1.09	0.79	1.50	0.59
Co-morbidity score				**0.07**								**0.22**
0	1.00				1.00				1.00			
1-2	1.22	0.95	1.58	0.12	1.08	0.81	1.45	0.59	1.21	0.90	1.64	0.20
3+	1.00	0.63	1.58	1.00	0.67	0.40	1.13	0.14	0.83	0.49	1.40	0.48
CCM missing	0.85	0.68	1.07	0.17	0.94	0.73	1.22	0.63	0.93	0.71	1.21	0.58
No HES link	1.05	0.83	1.34	0.66	1.13	0.86	1.48	0.39	1.19	0.91	1.58	0.21
Timely GP referral				**<0.001**				**<0.001**				**<0.001**
No GP referral	1.00				1.00				1.00			
FHA<=14 days	1.44	1.22	1.70	<0.001	1.47	1.21	1.78	<0.001	1.36	1.12	1.66	0.002
FHA>14 days	1.87	1.52	2.30	<0.001	1.45	1.15	1.84	0.002	1.33	1.05	1.70	0.02
Stage								**<0.001**				**<0.001**
I					1.00				1.00			
II					0.39	0.29	0.51	<0.001	0.40	0.30	0.53	<0.001
III					0.13	0.11	0.16	<0.001	0.14	0.12	0.17	<0.001
IV					0.04	0.03	0.05	<0.001	0.04	0.04	0.06	<0.001
Performance Status												**<0.001**
0									1.00			
1-2									0.53	0.44	0.64	<0.001
3-4									0.18	0.13	0.25	<0.001
Missing									0.47	0.35	0.64	<0.001

Table 12.6 (cont). Likelihood of still being alive 2 years after diagnosis, by selected patient, tumour and system factors for those diagnosed between 2006 and 2009 (DCO cases excluded) with stage recorded

Variable	Adjusted – IMD, age, sex, histology, year, CCM, stage, PS, timely referral, treatment type (n=5233, R^2=31.73)				Adjusted – IMD, age, sex, histology, year, CCM, stage, PS, timely referral, treatment type, timely 1st treatment (n=5233, R^2=32.04)			
	OR	95% CI		P	OR	95% CI		P
Deprivation quintile				**0.76**				**0.80**
1 (least deprived)	1.00				1.00			
2	1.02	0.74	1.40	0.92	1.01	0.73	1.39	0.97
3	1.08	0.79	1.47	0.64	1.07	0.78	1.46	0.67
4	0.90	0.67	1.21	0.51	0.91	0.67	1.22	0.51
5 (most deprived)	1.03	0.78	1.36	0.85	1.02	0.77	1.34	0.90
Age group				**0.69**				**0.67**
<60	1.00				1.00			
60-69	1.12	0.86	1.45	0.41	1.11	0.85	1.44	0.45
70-79	1.03	0.78	1.34	0.85	1.00	0.77	1.31	0.99
80+	0.95	0.68	1.33	0.79	0.94	0.67	1.31	0.71
Sex				**<0.001**				**<0.001**
Female	1.00				1.00			
Male	0.69	0.58	0.82	<0.001	0.69	0.58	0.82	<0.001
Histology				**0.0005**				**0.007**
NSCLC	1.00				1.00			
SCLC	0.48	0.31	0.74	0.001	0.55	0.35	0.85	0.008
Other	1.19	0.93	1.52	0.18	1.18	0.92	1.51	0.19
Year of Diagnosis				**0.43**				**0.41**
2006	1.00				1.00			
2007	1.02	0.75	1.38	0.91	1.00	0.73	1.36	0.99
2008	1.02	0.77	1.37	0.87	0.98	0.74	1.31	0.92
2009	0.82	0.59	1.14	0.24	0.79	0.57	1.11	0.18
Co-morbidity score				**0.02**				**0.02**
0	1.00				1.00			
1-2	1.35	0.99	1.84	0.06	1.35	0.99	1.84	0.06
3+	1.06	0.61	1.83	0.84	1.02	0.59	1.78	0.93
CCM missing	0.90	0.68	1.18	0.46	0.90	0.68	1.18	0.43
No HES link	1.40	1.04	1.88	0.03	1.40	1.05	1.89	0.02
Stage				**<0.001**				**<0.001**
I	1.00				1.00			
II	0.47	0.34	0.63	<0.001	0.47	0.35	0.64	<0.001
III	0.23	0.18	0.29	<0.001	0.24	0.19	0.30	<0.001
IV	0.09	0.07	0.12	<0.001	0.10	0.07	0.13	<0.001
Performance Status				**<0.001**				**<0.001**
0	1.00				1.00			
1-2	0.75	0.61	0.92	0.007	0.76	0.62	0.94	0.01
3-4	0.44	0.30	0.65	<0.001	0.46	0.31	0.67	<0.001
Missing	0.70	0.51	0.97	0.03	0.72	0.52	0.99	0.05
Timely GP referral				**0.14**				**0.16**
No GP referral date	1.00				1.00			
FHA<=14 days	1.23	1.00	1.52	0.05	1.22	0.99	1.50	0.06
FHA>14 days	1.16	0.90	1.50	0.25	1.15	0.89	1.48	0.29
Type of treatment				**<0.001**				**<0.001**
No treatment	1.00				1.00			
Surgery	11.24	7.78	16.24	<0.001	12.86	8.84	18.70	<0.001
Surgery +chemo/radiotherapy	13.13	8.78	19.63	<0.001	14.94	9.93	22.49	<0.001
Chemotherapy	2.48	1.70	3.62	<0.001	2.81	1.92	4.11	<0.001
Chemo+radiotherapy	4.75	3.41	6.61	<0.001	5.43	3.87	7.60	<0.001
Radiotherapy	2.24	1.67	3.00	<0.001	2.47	1.83	3.32	<0.001
Timely 1st treatment								**<0.001**
>31 days from diagnosis					1.00			
<31 days from diagnosis					0.63	0.51	0.79	<0.001

12.4 Discussion

12.4.1 *Principal findings*

Socio-economic inequalities in receipt of treatment appear to contribute to socio-economic inequalities in lung cancer survival. Survival inequalities were found when patient, tumour and system factors were included in the multivariable model but the addition of treatment type significantly attenuated socio-economic inequalities in survival. The further addition of time to treatment had no significant effect on socio-economic inequalities in survival. Time to treatment was, however, significantly associated with risk of death and those who received treatment within guidelines [within 31 days of diagnosis] had poorer survival than those who had later treatment [within 1 year of diagnosis].

12.4.2 *Strengths and weaknesses*

An exact date of death was not available as this was considered a potentially-identifiable data item. Survival time in weeks was utilised here.

Inconsistent recording of the date of diagnosis and the different methodology used for determining date of diagnosis in 2010, as previously described, might also be a problem when calculating survival time from diagnosis to death. However, the 2006-2009 dataset was used to calculate the likelihood of two-year survival, and both the 2006-2010 and 2006-2009 datasets were used to determine risk of all-cause mortality and similar patterns of results were found in both data-sets.

12.4.3 *Interpretation of results and comparison with other studies*

Inequalities in receipt of treatment [surgery and chemotherapy but not radiotherapy] were found for this dataset [chapter 10] and these treatment inequalities appear to substantially explain inequalities in survival. This has previously been shown in a small study of 695 patients that did not include co-morbidity or PS in the multivariable analysis (158). Number of co-morbidities and PS vary by SEP (69) and age (70) and might help explain socio-economic inequalities in receipt of treatment and survival. But in a multivariable analysis adjusted for stage and PS survival inequalities were still observed and it was only on addition of receipt of treatment that the association no longer remained significant. However, in the subset with stage recorded PS also

substantially accounted for socio-economic inequalities in survival. As previously discussed, this staged subset may not be representative of the full cohort, as patients within this were more likely to be younger and had higher rates of treatment.

It has been suggested that the poorer survival of UK cancer patients compared to the European average might be related to diagnostic delay (102). However, two literature reviews both found the evidence for any association between timely care and survival for lung cancer inconclusive (184, 185). Contradictory results were found in the studies examined but the quality of the studies included was mixed and most did not adequately control for important confounders such as age, stage, histology and co-morbidity (185). The lack of control for confounding factors may account for why those with more timely care actually had poorer survival, due to the Waiting Time Paradox [WTP], as previously discussed in chapter 11.

Adequately controlling for stage, co-morbidity and PS should therefore eliminate this 'sicker quicker' effect. In a small study of colorectal cancer patients, shorter diagnostic interval was associated with higher mortality for those who appeared more ill, but not for those presenting with 'vague' symptoms (179). However, in our study we found that a shorter diagnostic to treatment interval resulted in a lower likelihood of survival two years after diagnosis and increased hazard of death, compared to those with later treatment. Furthermore, those who had a FHA within 14 days of GP referral had poorer survival than those who waited longer to be seen in secondary care. These associations remained after age, stage, histology, co-morbidity and PS were taken into account in the multivariable analysis. It may be that uncontrolled confounding remains or that the measures of 'sickness' used – PS and co-morbidity - are not particularly good. The high levels of missing stage and PS data are also a major limitation. However, we also carried out this analysis in the staged subset [which is effectively a complete-case cohort for stage and PS] and a similar result was found.

The NHS Cancer Plan set guideline waiting times for cancer treatment of 31 days from diagnosis and 62 days from GP referral. I have previously shown that, in patients who received treatment within 1 year of diagnosis, those with later stage cancer, poor PS, and those undergoing chemotherapy as a first treatment were more likely to receive timely treatment within guidelines [chapter 11]. Those with higher SEP were not

significantly more likely to receive treatment within the 31 day guideline from diagnosis. It appears that sicker patients with later-stage cancer obtain non-curative treatment within guidelines whereas earlier stage, good-PS patients wait longer for curative care, but their survival is better.

Patients who were treated within the guideline targets had poorer survival than those who had later treatment, which might bring into question the clinical validity of these guidelines. Two year survival was better for those patients who had surgery later than the 31 day guideline [72.8% of those who had surgery between 31-62 days after diagnosis were still alive compared to 64.7% who had treatment within guidelines] but for four-year survival there was higher survival for those treated within guidelines [see Fig 12.10]. When I looked at time to surgery and survival for patients with early stage cancer [as these are the patients for whom application of the guidelines might improve survival] similar patterns were seen, so the evidence for the effectiveness of the guidelines in improving survival is unclear.

I previously found no socio-economic inequalities in the diagnosis to treatment interval but some suggestion of inequalities in the GP referral to FHA interval, with those in the highest and the lowest SEP groups having quicker referral. As no linear association is observed it is perhaps unsurprising that time from diagnosis to treatment had little effect on socio-economic inequalities in survival. A study that looked at breast cancer survival also found that that time to treatment was not associated with deprivation and that adjusting for time to treatment did not attenuate the association of deprivation with survival (181). They suggest that lower survival amongst more deprived patients may therefore relate to factors prior to their entry into the secondary care system although they were not able to consider inequalities in receipt of treatment as they looked at only those patients who received treatment.

The results from chapter 10 suggested that socio-economic inequalities in tumour type might account for some of the socio-economic inequalities in receipt of treatment as rates of treatment were higher for adenocarcinoma compared to squamous-cell tumours. The highest treatment rates were found in the ‘other-specified-histology’ and patients in this category had the highest two-year survival. However there was no

significant difference in two- year survival rates between patients diagnosed with adenocarcinoma and squamous-cell tumours.

12.4.4 *Implications for policy and practice, and further research*

Inequalities in receipt of treatment appear to substantially account for inequalities in lung cancer survival. However, clinical guidelines focus on target times for referral and treatment. Perhaps a clinical focus on ensuring that those who are eligible for treatment actually receive it, rather than on time-interval targets might have a greater impact on improving survival, as well as reducing inequalities in survival.

As patients who were treated within the guideline targets had poorer survival than those who had later treatment, the effectiveness of the guidelines on improving survival appears unclear. Patients with early stage cancer are likely to be the patients for whom application of the guidelines, resulting in earlier referral and treatment, might improve survival. Further research on this group of patients is warranted to help determine whether delays in referral and treatment lead to poorer lung cancer survival, without the confounding effect of the WTP. Further research is also required to determine whether this interval effect on survival is also seen in other cancers.

Further examination of the patient, tumour and system factors that determine timeliness of treatment is warranted to determine why those who have later treatment have better survival, and to develop interventions to improve cancer survival.

12.5 Chapter summary

Socio-economic inequalities in lung cancer survival appear to be statistically explained by inequalities in receipt of treatment but not by time from GP referral to FHA or from diagnosis to treatment. However, patients who were treated within the time-to-treatment guideline targets had poorer survival compared to those who had later treatment, as explained by the WTP.

Interventions that address socio-economic inequalities in receipt of treatment are likely to reduce socio-economic inequalities in survival and thus improve survival rates overall.

The next chapter will summarise and discuss all the findings from previous results chapters on socio-economic inequalities in: receipt of treatment [chapters 7 and 10]; referral, diagnostic and treatment intervals [chapter 11]; and survival [chapter 12]; discuss the methodological strengths and weaknesses of the study, the implications for policy and practice, and the further research required.

Chapter 13. Overall summary - discussion and conclusions

This final chapter presents a summary of the thesis findings, details overall strengths and weaknesses of the data and the analyses, and suggests some detailed further research that might arise from this work, as well as the specific post-doctoral research that I plan to conduct. The findings from each component of the thesis in relation to published studies have been discussed in depth in previous chapters and so a summary of what the thesis has added to knowledge will be detailed here.

13.1 Background

This research examined the evidence for socio-economic inequalities in time to, and receipt of, treatment for lung cancer, and the contribution of these inequalities to socio-economic inequalities in survival, using the intervention-generated inequalities framework.

13.2 Methods

To examine the existing evidence for socio-economic inequalities in lung cancer treatment a systematic review and meta-analysis of published studies was conducted. Cohort studies of participants with a primary diagnosis of lung cancer [ICD10 C33 or C34], where the outcome was receipt of treatment [rates or odds of receiving treatment] and where the outcome was reported by a measure of socio-economic position were examined. A quality tool was used to assess study quality. Studies conducting multivariable analysis were considered for meta-analysis.

Potentially-important confounders that had previously been poorly investigated were identified by the systematic review and the results from this were used to determine variables to include in the secondary data analyses. Cancer registry [NYCRIS], Hospital Episode Statistics [HES] and lung cancer audit [LUCADA] data-sets were linked in order to investigate intervention-generated inequalities in lung cancer care.

NYCRIS data for 65,210 patients diagnosed between 1999 and 2010 with a primary diagnosis of lung cancer were analysed. Logistic regression was used to examine the likelihood of receipt of treatment by SEP and of receiving timely referral, diagnosis and treatment within guideline targets, as well as the likelihood of still being alive two

years after diagnosis, by SEP. Cox regression was used to assess the likelihood of early referral, diagnosis and treatment and risk [hazard] of death by SEP.

13.3 Results

A total of 46 papers were included in the systematic review and 23 in the meta-analysis. Socio-economic inequalities in receipt of lung cancer treatment [surgery, chemotherapy but not radiotherapy] were identified in the meta-analysis. These inequalities could not be accounted for by socio-economic differences in stage at presentation or by differences in health care system. However, not all of the included studies reported details of stage and histology, both of which influence treatment type, and very few studies took co-morbidity or performance status into account.

In the linked database analysis socio-economic inequalities in receipt of surgery and chemotherapy, but not radiotherapy, were found after control for age, sex, histology, stage, performance status and co-morbidity. The odds of receiving surgery were significantly lower in the lowest compared to the highest SEP group. Patients in the lowest SEP group were significantly less likely to receive chemotherapy in the full 2006-2010 cohort but not in the staged-subset when performance status was included in the model.

In the 2006 to 2010 cohort 70% of patients received a hospital appointment within the 14 day urgent referral target [although patients with non-urgent referrals might also be included here]. Time to treatment targets were only being met for 42.5% when measured from diagnosis and for 62% from GP referral. Socio-economic inequalities in time from GP referral to FHA were identified but a linear trend association by SEP was not seen. Late-stage, poor performance status, high SEP and SCLC histology were associated with a higher likelihood of a first hospital appointment within 14 days of GP referral. Older patients were less likely, whereas late stage and poor PS patients were more likely, to receive treatment within guideline time limits.

Only 15.3% of patients were still alive 2 years after diagnosis. This increased to 70% for those who had surgery. Patients referred and treated later than guideline targets had higher likelihood of surviving to 2 years and decreased risk of death.

Socio-economic inequalities in survival were found in a multivariable analysis controlling for age, sex, histology, year of diagnosis, timely GP referral, co-morbidity, stage and performance status, with those in the lowest socio-economic group significantly less likely to be alive after 2 years, compared to the highest group. However, when receipt of treatment was included in the analysis the association no longer remained significant. Addition of timeliness of treatment made no difference to the conclusion.

13.4 Discussion

13.4.1 *Principal findings*

This study found socio-economic inequalities in the lung cancer care pathway, with inequalities in receipt of surgery and chemotherapy, and in the time interval from GP referral to FHA. Socio-economic inequalities in survival from lung cancer were statistically explained by socio-economic inequalities in receipt of treatment, but not by inequalities in timeliness of referral and treatment, in this cohort.

Socio-economic inequalities in lung cancer treatment could not be explained by inequalities in stage or performance status in the full dataset. However, socio-economic differences in performance status may account for the observed socio-economic differences in receipt of chemotherapy in the staged subset. Socio-economic inequalities in tumour type may account for some of the socio-economic gradient in surgery.

Socio-economic inequalities in the GP referral to FHA, diagnosis and treatment intervals were found but were not seen in the interim intervals from FHA to diagnosis or from diagnosis to treatment, suggesting that interval inequalities originate in the GP referral to FHA interval. However, no survival benefit of timely referral and treatment was demonstrated and patients who were treated within the guideline targets had poorer survival than those who had later treatment.

13.4.2 *Methodological strengths and weaknesses*

This is one of the first studies to link three datasets [NYCRIS, HES and LUCADA] in order to examine the factors that may influence socio-economic inequalities in lung cancer treatment, time to treatment and survival. Using a triple-linked dataset allowed

inclusion of co-morbidity, stage and performance status data in the analyses whilst also employing the large, comprehensive cancer registry dataset. However, the years in which stage and PS were most completely recorded in LUCADA [2009-2010] were also the years of registry data which did not yet have a co-morbidity score available. Examining receipt of treatment and survival in the 2006-2008 dataset that included all three variables gave the same pattern of results [results not shown] as that for 2006-2009 and 2006-2010, therefore the larger year groups were employed where possible.

Co-morbidity was included in the 1999-2005 cohort analysis, and stage and PS in the 2006-2010 cohort, with the addition of co-morbidity to see if this made any difference to the outcome. Differences over time between the earlier- and later-year cohorts could also be observed.

A major strength of this study is the completeness of treatment data recorded in the large NYCRIS cancer registry dataset particularly for chemotherapy and radiotherapy, which are often poorly recorded elsewhere. Treatment was also more comprehensively recorded here than in LUCADA (253).

LUCADA data has been cited as an ideal data source for lung cancer research (153) but although LUCADA audit data completeness has improved, nationally this was low in the early years [66% entry of patients diagnosed in 2006, increasing to 93% entry in 2010] (246). The number with stage recorded was also initially low [36% of patients diagnosed in 2006] but again is increasing over time [79% in 2010] (246). For my linked north of England dataset the numbers were lower than this. Stage and PS were available within the linked LUCADA data but only 27% [7769] of the 2006-2010 registry cohort had stage recorded in LUCADA. Therefore one major weakness of the analysis was the high level of missing stage and PS data.

Stage was recorded for 11.8% in 2006 and data completeness improved over time. However, even in 2010, the year with the most complete stage data, stage was only recorded for 43% of participants. Multiple imputation was considered as a way of dealing with missing data but it is not recommended where over 50% of the data in a variable are missing (241). An alternative way to address the problem of missing data is to analyse only complete cases, although results from complete-case analyses can be biased (242). Therefore I looked at the subset of patients who had stage recorded

[as an analysis of complete-case stage patients] and I also analysed the full dataset and included a 'stage missing' category. Differences between the datasets were examined and used to help explain any differences in outcome observed.

Patients with poorer performance status had increased odds of timely FHA, diagnosis and treatment but a lower likelihood of receiving treatment. No clear-cut pattern was observed in time intervals or receipt of treatment by co-morbidity score in this study. Both co-morbidity score and PS can be used as proxy measures of general wellbeing and my results would suggest that PS may be a better marker of this. PS is a measure of patients' functional status and need for care measured on an ECOG scale of 0-4, determined by the care team. Although it has been shown to have good prognostic predictive validity (257) it could be considered a somewhat subjective measure. Only moderate inter-observer agreement in allocating PS score was found in an inter-observer variability study, although there was good agreement when allocating good [PS 0-2] compared to poor PS [PS 3-4] (258).

Co-morbidity score, obtained from HES data, does not appear to be a particularly good measure of patient well-being, and high levels of missing data were an issue. The Charlson Co-morbidity [CCM] Index is a validated instrument for measuring co-morbidity (245) but only contains details of conditions requiring in-patient care. Patients who suffer from a relevant condition but are treated by their GP will have a score of O, thus resulting in misclassification and underestimation of co-morbidity (259). It is also a crude measure of co-morbidity as patients with mild and severe forms of a disease receive the same score. This is a problem for conditions such as COPD where the severity of the disease is likely to influence the likelihood of surgery (259). Details of the particular condition and the severity of this would be a more useful measure than a crude score. Details of co-morbidity are included within the LUCADA audit dataset although recording of this remains low. One of the key messages of the 2012 audit report (246) related to improving the recording of co-morbidity so that this is a more reliable variable for case-mix adjustment. Future studies may therefore be able to utilise this.

As for most cancer registry-based analyses, an area-based, ecological measure of SEP, calculated using postcode, was employed, which is unlikely to be an accurate marker

of individual circumstances and access to resources (234), potentially under-estimating the strength of the true association between SEP and receipt of treatment. A changing-deprivation-score-over-time methodology was used, as this is more likely to accurately reflect current area deprivation, rather than previous methods which retrospectively applied current deprivation back in time to earlier years of diagnosis (244).

Lack of smoking status data is a major weakness for any study examining lung cancer but is one found for all studies examined as part of this research, as smoking status is not routinely recorded as part of the cancer registry dataset.

The focus of this PhD study was lung cancer. One advantage of focusing on a single cancer is that a detailed and in-depth analysis can be carried out within the three-year timescale, which would not be possible if the scope of the PhD were broader. Conducting analyses on a combined number of different cancers may mask any between-cancer differences relating to tumour development and prognosis that might influence likelihood and timing of treatment. However, the generalisability of the results to other cancers is unclear.

The systematic review and meta-analysis included studies from UHCS and non-UHCS countries and so the results are relevant internationally. However, for the secondary data analysis, local north of England data were analysed. Local rather than England-wide data were requested from NYCRIS following discussion with the NYCRIS Director and a number of analysts. This was a pragmatic decision relating to the complexity of the linkage, and the manageability and size of the dataset, but affects the potential generalisability of these lung cancer results for the whole of England, the UK and beyond.

13.4.3 *Interpretation of findings and comparisons with other studies*

I have previously interpreted the findings of each of my study components and done a comparison with published studies in the preceding chapters. Here I will make some remarks in summary.

Overall, this study has been able to advance knowledge on the topic of socio-economic inequalities in lung cancer care. I have demonstrated socio-economic inequalities in lung cancer treatment for surgery and chemotherapy, but not radiotherapy, in both

UHCSs and non-UHCSs, in my systematic review and meta-analysis. I have been able to include a number of important confounders that have not been previously well examined [stage, PS, co-morbidity] in the secondary data analysis, although the levels of missing data were a limitation. Inequalities in the referral, diagnostic and treatment intervals have not been well explored before. My results suggest that socio-economic inequalities are found in the referral interval. I have also been able to show an association between socio-economic inequalities in receipt of treatment and inequalities in lung cancer survival.

13.4.4 *Implications for policy and practice, and further research*

I have been able to investigate a number of factors that may be important in the relationship between SEP and survival such as receipt of, and time to, treatment, stage and performance status. However, high levels of missing data and inconsistent data recording remain important problems. In order to clearly document the relationships between these variables and receipt of treatment and survival, more complete and accurate recording of data is required.

The high levels of missing stage and PS data within the early LUCADA data were a major problem. The comparability of the audit data with that held within registries is uncertain as differences were found between trusts that supplied high and low levels of data to the audit in early years (152) that does appear to have been somewhat glossed over in the literature. Data quality and completeness within LUCADA has greatly improved over recent years [see appendix B Fig B1] and this is now an excellent resource that will allow better investigation into lung cancer inequalities in the future.

A new single national cancer registration system [Encore] was launched in 2013 in order to improve timeliness and quality of the data, reduce data replication and the costs involved in this, and to support the improvement of staging information (260). The data will be used in conjunction with, or as an alternative to, the existing cancer audits including LUCADA. Therefore, Encore appears to be a potential resource that will improve the quality of research into inequalities in lung cancer care.

Smoking status is not recorded in the cancer registry dataset but is available from primary care data. Date of first contact with GP, which could be used to calculate the

primary care interval [from first patient presentation to GP referral] could also be obtained from this source. Further linkage of my secondary care linked-dataset to primary care data could allow further exploration of where on the lung cancer care pathway inequalities might occur and also allow the inclusion of smoking status in analyses, the omission of which is a major weakness in current studies.

Socio-economic inequalities in were found in the lung cancer care pathway but it is still unclear whether these inequalities are also found for other cancers and whether they occur at the same points in the care pathway. Similar analyses should, therefore, be conducted for other cancers.

Interventions that address socio-economic inequalities in receipt of treatment are likely to reduce socio-economic inequalities in survival and thus improve the overall likelihood of survival. Further research is required to investigate the unexplained variance in treatment rates, looking at factors such as patient choice, doctor-patient communication of risk and benefit, and possible variation by trusts or within this, by hospital and individual clinician. I hope to examine these factors in my post-doctoral work.

13.4.4.1 Further research - post-doctoral work

My systematic review on socio-economic inequalities in lung cancer treatment has been published in an international journal (236) and press coverage on this paper resulted in an invited editorial (261). Papers are in preparation on the empirical work presented in chapters 10-12 and the preliminary findings have been presented at conferences and published in abstract form (262-264). The rapid reviews of the evidence on socio-economic inequalities in referral, diagnostic and treatment intervals [chapter 4, table 4.1], and in survival [chapter 5, table 5.1], conducted as part of the literature review, will also be developed into full systematic reviews for publication.

As a member of Fuse [UKCRC Centre for Translational Research in Public Health], I hope to feedback the findings from this thesis to practitioners and policy makers with support from the Fuse Knowledge Exchange Broker, who has an explicit remit for knowledge translation. Further qualitative work with healthcare professionals to explore potential reasons for inequalities in receipt of treatment, as well as the

implications for clinical practice of earlier referral and treatment resulting in poorer survival, are also planned.

A future NIHR Fellowship application, to further investigate intervention-generated inequalities in cancer care using a mixed-methods approach, is planned. It is hoped to examine doctor-patient communication using a series of vignettes, and to conduct multi-level modelling on the linked data-set to take better account of surgeon and hospital characteristics in receipt of care.

It is planned to repeat the secondary-data analyses detailed in this thesis on NYCRIS colorectal cancer data linked to HES data. The linked colorectal dataset was obtained at the same time as the lung cancer data and ethical approval is in place to begin this work immediately.

13.5 Reflections on the PhD process

During the PhD I wrote a number of blog posts for the Fuse Open Science blog, detailing some of the many highs (265), and lows [problems with obtaining the secondary data] (266), of the PhD experience, and also why I decided to undertake a PhD (267).

13.6 Chapter summary and overall conclusions

Intervention-generated inequalities in lung cancer care were identified from this research. Socio-economic inequalities in receipt of surgery and chemotherapy, but not radiotherapy, were found in the systematic review and meta-analysis and in the secondary data-analysis. Socio-economic inequalities in lung cancer treatment could not be explained by inequalities in stage or performance status in the full dataset. However, socio-economic differences in performance status may account for the observed socio-economic differences in receipt of chemotherapy in the staged subset. Tumour type may account for some of the socio-economic gradient in surgery.

Socio-economic inequalities in the GP referral to FHA interval were found. Socio-economic inequalities in survival from lung cancer were statistically explained by socio-economic inequalities in receipt of treatment, but not by inequalities in timeliness of referral and treatment, in this cohort.

Suggestions have been made for future research that could help confirm these thesis findings, with respect to where on the pathway of lung cancer care inequalities occur, and also why they might occur. It will then be possible to develop specific interventions that address socio-economic inequalities in receipt of treatment and reduce socio-economic inequalities in survival.

Chapter 14. Appendices

14.1 Appendix A: Variables requested from NYCRIS

Table A.1. Variables that are held in the NYCRIS regional dataset, or can be derived from this

Variable	Derived from NYCRIS variable (by NYCRIS)	Reason for inclusion	Analyses to be used in
IMD ranking	Postcode	The project is looking at inequalities by SEP and so a measure of SEP is required	All analyses, as the measure of SEP
Age at diagnosis	Date of birth/ Date of Diagnosis	Age has been shown to influence receipt of treatment and so will be included as a confounder. Age at diagnosis is required to calculate survival time.	Logistic regression analyses of rates of treatment, Cox proportional hazard models of survival and time to treatment
Year of diagnosis	Date of diagnosis	Treatment trends may change over time	Logistic regression analyses of rates of treatment, Cox proportional hazard models of survival and time to treatment
Sex	Sex	Sex is included as a potential confounder	Logistic regression analyses of rates of treatment, Cox proportional hazard models of survival and time to treatment
Marital status	Marital status	Marital status may affect survival and so will be included as a confounder	Logistic regression analyses of rates of treatment, Cox proportional hazard models of survival and time to treatment
Age at death	Date of Death/ Date of Birth	Required to calculate survival time (age at death – age at diagnosis)	All survival models
Cause of Death = lung cancer (Y/N)	Cause of Death	Need to differentiate between those who died of cancer of interest and those who died of other causes	Survival models
DCO (Y/N)	DCO	Need to differentiate between those who were DCO and those who weren't	Logistic regression analysis comparing profile of those who are DCO with those who are not
Cancer site (ICD10 C33, C34 (lung cancer)	Cancer site	These are the cancer sites that the project will investigate	Incidence, rates of treatment, time to treatment and survival analyses
Cancer type	Cancer morphology/ type	Cancer morphology may influence survival and type of treatment received	Logistic regression analyses of rates of treatment, Cox proportional hazard models of survival and time to treatment

Table A.1 (cont). Variables that are held in the NYCRIS regional dataset, or can be derived from this

Variable	Derived from NYCRIS variable (by NYCRIS)	Reason for inclusion	Analyses to be used in
Basis of diagnosis	Basis of diagnosis	Basis of diagnosis may influence time to treatment. Want to look at rates of treatment for histologically-confirmed cases.	Logistic regression analyses of rates of treatment, Cox proportional hazard models of time to treatment
Date of GP referral	Date of GP referral	Required to calculate primary care delay and investigation delay	Cox proportional hazard models of time to referral and 2^0 care investigation
Date of first hospital appt	Date of first hospital appt	Required to calculate investigation delay and diagnostic delay	Cox proportional hazard model of time to 2^0 care investigation and diagnosis
Date of diagnosis	Date of diagnosis	Required to calculate diagnostic delay and treatment delay	Cox proportional hazard models of time to diagnosis and treatment
Date of first surgery	Date of surgery	Required to calculate treatment delay and therapy delay	Cox proportional hazard models of time to treatment and therapy
Date of first chemotherapy	Date of chemotherapy	Required to calculate therapy delay	Cox proportional hazard models of time to therapy
Date of first radiotherapy	Date of radiotherapy	Required to calculate therapy delay	Cox proportional hazard models of time to therapy
Trust: (in pseudo-anonymised form as trust A,B,C etc)	PCT code	Receipt of, and time to, treatment may be determined by Trust factors and so this will be included as a confounder	Multi-level modelling
Surgeon: (in pseudo-anonymised form as surgeon 1,2,3 etc)	Consultant code	Survival may be associated with surgeon and so this will be included as a confounder	Multi-level modelling All survival analyses

Table A.2. Variables that are available from the linked, anonymised, regional subset of NYCRIS and HES data, or that can be derived from them

Variable	Derived from HES variable (by NYCRIS)	Reason for inclusion	Analyses to be used in
Charlson co-morbidity score (CCS)	Charlson co-morbidity score (in NCDR)	Co-morbidity may influence receipt of treatment and survival and so will be included as a confounder	Logistic regression analyses of rates of treatment, Cox proportional hazard model of survival
Nature of admission (elective/emergency)	Method of Admission	Nature of admission may influence survival. Emergency rather than elective admission may be a marker of late presentation	Logistic regression analysis comparing profile of those who are emergency admissions with those who are not, Cox proportional hazard model of survival
Post-operative complications	Diagnostic codes ?	Post-operative complications may contribute to delay from surgery to adjuvant therapy and influence survival	Cox proportional hazard models of survival and time to adjuvant treatment
Ethnicity	Ethnic category	Ethnicity may influence receipt of treatment and so will be included as a confounder	Logistic regression analyses of rates of treatment, Cox proportional hazard models of survival and time to treatment
GP(in pseudo-anonymised form as GP a,b,c etc)	Referring general medical practitioner	GP may influence referral time (primary care delay)	Cox proportional hazard models of time to treatment

Table A.3. Variables available from the linked NYCRIS regional lung cancer and LUCADA dataset

Variable	Derived from LUCADA variable (by NYCRIS)	Reason for inclusion	Analyses used in
Performance status	Performance status	Performance status may influence receipt of treatment and survival and so will be included as a confounder	Logistic regression analyses of rates of treatment, Cox proportional hazard model of survival
Stage	Stage	Stage has been associated with receipt of treatment and survival and so will be included as a confounder	Logistic regression analyses of rates of treatment, Cox proportional hazard model of survival

14.2 Appendix B: Data linkage and data completeness

Table B.1. Completeness of stage data in the linked dataset, by year

	Stage										
Year	**1**		**2**		**3**		**4**		**missing**		**Total**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
1999	0	0	0	0	0	0	0	0	5,154	100	5,154
2000	0	0	0	0	0	0	0	0	5,227	100	5,227
2001	0	0	0	0	0	0	0	0	5,200	100	5,200
2002	0	0	0	0	0	0	0	0	5,219	100	5,219
2003	0	0	0	0	0	0	0	0	5,221	100	5,221
2004	0	0	0	0	1	0.02	0	0	5,215	99.98	5,216
2005	2	0.04	0	0	0	0	1	0.02	5,237	99.9	5,240
2006	129	2.3	45	0.8	229	4.1	268	4.7	4,862	88.2	5,533
2007	151	2.6	73	1.2	274	4.7	368	6.3	4,846	85.2	5,712
2008	229	3.8	86	1.4	464	7.8	777	13.0	4,295	74.0	5,851
2009	355	6.0	128	2.2	620	10.4	1,037	17.4	3,731	64.1	5,871
2010	322	5.5	220	3.7	686	11.7	1,308	22.2	3,230	56.9	5,766
Total	**1,188**	**1.8**	**552**	**0.8**	**2,274**	**3.4**	**3,759**	**5.6**	**57,437**	**88.4**	**65,210**

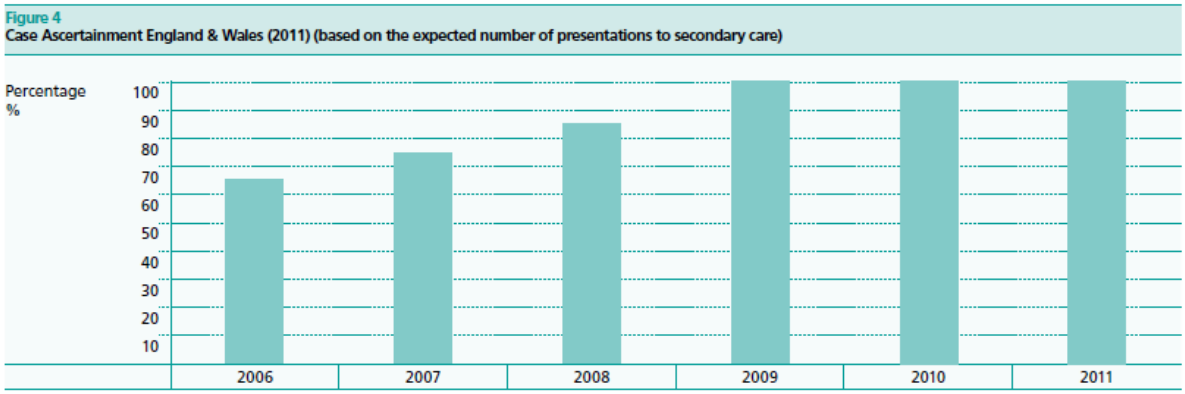
Table B.2. Completeness of performance status data in the linked dataset, by year

	Performance Status												
Year	**0**		**1**		**2**		**3**		**4**		**missing**		**Total**
	N	**%**	**N**	**%**	**N**	**%**	**N**		**N**	**%**	**N**	**%**	
1999	0	0	0	0	0	0	0	0	0	0	5,154	100	5,154
2000	0	0	0	0	0	0	0	0	0	0	5,227	100	5,227
2001	0	0	0	0	0	0	0	0	0	0	5,200	100	5,200
2002	0	0	0	0	0	0	0	0	0	0	5,219	100	5,219
2003	0	0	0	0	0	0	0	0	0	0	5,221	100	5,221
2004	0	0	1	0.02	0	0	0	0	0	0	5,215	99.98	5,216
2005	1	0.02	1	0.02	1	0.02	1	0.02	0	0	5,236	99.9	5,240
2006	219	4.0	301	5.4	192	3.5	139	2.5	26	0.5	4,656	84.2	5,533
2007	253	4.4	374	6.6	214	3.8	152	2.7	48	0.8	4,671	81.8	5,712
2008	332	5.7	598	10.2	402	6.9	341	5.8	107	1.8	4,071	69.6	5,851
2009	494	8.4	807	13.8	526	9.0	432	7.4	170	2.9	3,442	58.6	5,871
2010	544	9.4	883	15.3	568	9.9	539	9.4	224	3.9	3,008	52.2	5,766
Total	**1,843**	**2.8**	**2,965**	**4.6**	**1,903**	**2.9**	**1,604**	**2.5**	**575**	**0.9**	**56,320**	**86.4**	**65,210**

Table B.3. Completeness of HES linkage in the linked dataset, by year

	HES link				
	No		Yes		
Year	N	%	N	%	Total
1999	596	11.6	4,558	88.4	5,154
2000	600	11.5	4,627	88.5	5,227
2001	570	11.0	4,630	89.0	5,200
2002	442	8.5	4,777	91.5	5,219
2003	474	9.1	4,747	90.9	5,221
2004	416	8.0	4,800	92.0	5,216
2005	425	8.1	4,815	91.9	5,240
2006	490	8.9	5,043	91.1	5,533
2007	442	7.7	5,270	92.3	5,712
2008	675	11.5	5,176	88.5	5,851
2009	5,758	98.1	113	1.9	5,871
2010	5,663	98.2	103	1.8	5,766
Total	**16,551**	**25.4**	**48,659**	**74.6**	**65,210**

Figure B.1. LUCADA case ascertainment, and stage & performance status data completeness, for England and Wales, by year [246]



Figures taken from National Lung Cancer Audit Report 2012

14.3 Appendix C: Supporting Information for chapter 7

Appendix C1. Protocol

Summary

Background

Intervention-generated inequalities are health inequalities that result from the way that health interventions are organised and delivered and there is some evidence to suggest that intervention-generated inequalities in care may occur for some common cancers. Although the incidence and outcome of lung cancer varies with socio-economic position, it is not known whether inequalities in treatment occur and, if they do, how these might contribute to inequalities in outcome.

Review objectives

To summarise the existing literature and assess whether there are socio-economic differentials in receipt of treatment for lung cancer

Population

Adults who have a primary diagnosis of lung cancer [ICD10 C33 and C34], participating in studies published in a peer-reviewed journal up to 2011, and where the relevant outcome is analysed according to a measure of socio-economic position [including an individual or area-based measure of socio-economic position, deprivation, income, or education].

Interventions and comparators:

Receipt of any curative or palliative treatment for lung cancer including surgery, chemotherapy and radiotherapy compared to not receiving surgery, chemotherapy or radiotherapy

Outcomes:

i) Rates of treatment; or ii) Odds of receiving treatment; looking at low [most deprived] compared to high [least deprived] SEP or trends by socio-economic strata

Study design:

Cohort, observational studies conducting appropriate univariable or multivariable analyses

C1.1 Background

C1.1.1 *Lung cancer*

Worldwide, lung cancer is the most common cancer. In the UK it is the second most common cancer for incidence overall [the second most common for men and third most common for women] (8), as well as the most common cause of cancer mortality (9). Less than 10% of those diagnosed survive for 5 years.

Lung cancers are classified into small cell [SCLC] and non-small cell [NSCLC] cancers, with NSCLC accounting for 80% of lung cancers. NSCLC can be further divided into squamous cell carcinomas, adenocarcinomas and large cell carcinomas (18). NICE guidelines recommend radical surgery [pneumonectomy or lobectomy] for stage I or II NSCLC. Chemotherapy and radical radiotherapy are recommended for stage IIIa, with chemotherapy for stage IIIb and good performance-status stage IV lung cancer patients. Radiotherapy may be given as a palliative option for stage IV patients with poor performance status (18). Intervention with surgery, chemotherapy or radiotherapy has been shown to improve survival (18).

The incidence and outcome rates of lung cancer vary with socio-economic position [SEP], with incidence and mortality rates 2-3 times higher in the more deprived, within the UK (8). A strong deprivation gradient for incidence (16) and mortality is also seen worldwide. However, it is not known whether inequalities in investigation and treatment occur and, if so, how these might contribute to inequalities in outcome.

C1.1.2 *Intervention-generated inequalities*

Intervention-generated inequalities are health inequalities that result from the way that health interventions are organised and delivered (7) so that although overall health may improve as the result of an intervention, differences in access to the intervention, differential uptake and delays in uptake might result in inequalities in outcome. Inequalities are likely to occur at many different stages of intervention pathways and act in a cumulative way. It is also likely that intervention-generated inequalities contribute to overall socio-economic inequalities in morbidity and mortality, although this has not been conclusively demonstrated (7).

Inequalities in cancer care within the UK have been noted and the NHS Cancer Plan in 2000 pledged to reduce cancer mortality, reduce delay in diagnosis and treatment and increase survival whilst acting to reduce inequalities (24). More recently the National Cancer Equality Initiative has been set up to address some of these issues (10). This is an important task as, in a 2006 review that summarised a decade of research on the association between socio-economic status and cancer survival, the authors suggested that socio-economic differences in 'access to optimal treatment' (26) might at least partially explain survival differences.

Inequalities in access to cancer care have been shown in individual studies for a number of cancers and in a non-systematic review for colorectal cancer (11) but the evidence is inconclusive and there has been no systematic review of the evidence to demonstrate if such inequalities in access to care exist for lung cancer.

C1.2 Review Objectives

To summarise the existing literature and assess whether there are socio-economic differentials in receipt of treatment for lung cancer

C1.3 Methods

C1.3.1 *Search strategy*

Systematic methods will be used to identify relevant studies, assess study eligibility for inclusion and evaluate study quality. A search will be undertaken to locate all studies published up to May 2011 examining care and treatment for lung cancer associated with socio-economic status. One researcher [LF] will develop the search strategy with support from her supervisors, which will then be refined with the help of a medical librarian and used to search the online databases of MEDLINE, EMBASE and Scopus. Slightly different strategies will be required for each database [for example MEDLINE recognises the MESH term Lung Neoplasms/ whereas EMBASE does not and uses Lung cancer/. See pp6-8 of this protocol for draft MEDLINE and EMBASE search strategies]. Additional studies will be identified by reviewing the reference lists of relevant studies identified from the search and by using a forward citation search to identify more recent studies that have cited an older, relevant study. EndNote software will be used to manage the references.

C1.3.2 *Study Eligibility*

Cohort studies of adult participants who have a primary diagnosis of lung cancer [small-cell lung cancer or non-small-cell lung cancer - ICD10 C33 or C34], published in a peer-reviewed journal up to 2011, and where the outcome is receipt of care or treatment [measured by rates or odds of receiving care/treatment] and where the outcome is analysed by a measure of socio-economic position [such as an individual or area-based measure of SEP, deprivation, income or education] will be eligible for inclusion. Receipt of any curative or palliative treatment for lung cancer including surgery, chemotherapy and radiotherapy will be considered.

Preliminary independent screening of the titles and abstracts obtained from the database searches will be carried out by two researchers [LF and HW]. Initial screening of titles will be carried out to remove obviously irrelevant papers. However, from a preliminary scoping review by LF, the early pilot searches recovered studies that, although they conducted analyses by SEP, did not always mention this in the abstract or title. Therefore, in the title search, any titles that refer to surgery, chemotherapy and radiotherapy uptake for lung cancer will be retained. Papers that look at disparities in cancer survival/mortality will also be included as further checking of the abstract is required to see if inequalities in access to treatment are also examined.

Selected abstracts will then be screened and a subset of studies will be selected for further review and the full article obtained. Abstracts that refer to socio-economic inequalities in receipt of care/treatment will be retained. Abstracts that refer to racial, ethnic, geographical, sex and age-related disparities in treatment as well as disparities by insurance type will also be retained as often these papers also look at SEP, even if this is not mentioned in the abstract. Papers that look at delay will not be included. Two researchers [LF and HW] will then independently assess the selected full papers for eligibility according to the study-eligibility criteria detailed above. Any disagreements at any of the screening stages will be resolved by discussion between the two reviewers in the first instance. If agreement cannot be reached, then a third reviewer [JA or MW] will independently review the title, abstract or full paper, as appropriate, and a majority decision will be taken on inclusion/exclusion.

C1.3.3 *Data Extraction*

Data extraction will be carried out by LF and HW using a pro-forma to be developed by LF for this purpose. Data relating to study authors, journal, study design, year of study, data source, number of participants, years of diagnosis, measure of SEP, confounding variables included in the analysis [such as age, sex, stage, co-morbidities, cancer type/site, vital/performance status, marital status, smoking status, cancer network, health board, hospital, emergency or elective treatment, distance from hospital/travel time, ethnicity, insurance status], type of treatment received [any, surgery, chemotherapy, radiotherapy], statistical tests carries out, outcome measures [treatment rates or odds of treatment], comparator used, significance [p values], precision [confidence intervals], other variables that were significant; will be recorded.

There is evidence to suggest that insurance status is an important factor relating to access to lung cancer care in the US system (188) but is less relevant or rarely measured in the UK and Europe. Therefore studies will be split into three categories: those carried out in a healthcare system free at the point of access [similar to the UK]; those based on an insurance system [similar to the USA]; those that include a mixture of free care and social insurance-based payment [some European systems] (189).

C1.3.4 *Study Quality*

Study quality will be appraised using criteria based on the SIGN guidelines (192) and the STROBE [Strengthening the Reporting of Observational Studies in Epidemiology] guidelines (194) that contain a checklist of 22 items that should be included in cohort studies. Although the STROBE guidelines are a checklist measure of good reporting rather than 'an instrument to evaluate the quality of observational research' (194) , a number of other lung cancer systematic reviews use a similar scale for quality ascertainment (185, 188).

The quality of reporting on the following criteria will be assessed: study design, size, setting, dates, data sources, eligibility criteria, number of participants potentially eligible, number actually included, number analysed, missing/incomplete data reported, variables included [in terms of outcome, exposure, predictors, confounders], type of statistical analysis carried out, unadjusted and adjusted estimates reported,

precision [confidence intervals], significance [p values] given, limitations of the study, potential bias addressed, external validity of results and funding source.

C1.3.5 *Statistical analysis*

Meta-analysis will be considered if there are sufficient studies available with suitable data. If it is not possible to conduct a meta-analysis, due to the heterogeneity of the studies, then Harvest Plot methodology will be considered. This is a method that has been devised for synthesising evidence from studies looking at the differential effects of interventions, where meta-analysis is not suitable (196). Meta-regression may also be considered if there are sufficient studies with similar variables available that might enable combined analysis of factors associated with combined outcomes.

Table C2.1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported in section paragraph #*
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Para 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Para 1-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Para 1-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Para 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Para 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Para 2-3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Para 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S1

Table C2.1 (cont). PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported in section paragraph #
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Para 3-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Para 8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Para 3-7, 9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Para 10-11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Para 13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Para 14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

#*: paragraphs refer to paragraphs within PLoS Medicine paper generated from this research (236)

Appendix C3. Search strategies

Table C3.1. MEDLINE search strategy 05/05/11

	Search Term	Number Retrieved
1.	Lung Neoplasms/ di, ep, mo, pc, rt, su,	59693
2.	Exp carcinoma, Non-Small-cell Lung/or exp Carcinoma, Small Cell/	37049
3.	Or/1-2	80591
4.	Social Class/ or Socio-economic Factors/	110317
5.	Socio-economic status.mp	4098
6.	Education/ or exp Education, Continuing	64913
7.	Income/cl, sn	3109
8.	Exp Health Status/sn, td	1046
9.	Exp Poverty/pc, sn, td	2309
10.	Exp Social Class/	27097
11.	Socio-economic position.mp	213
12.	Inequalities.mp	5837
13.	Exp Social Environment/td	137
14.	Social factors.mp	4869
15.	Income.mp	53934
16.	Exp Residence Characteristics/cl, sn	3307
17.	Social Class.mp	29869
18.	Education.mp	463082
19.	Exp Health Status Disparities/	3380
20.	Inequities.mp	1569
21.	Deprivation.mp	51228
22.	Equity.mp	5183
23.	Inequity.mp	920
24.	Insurance status.mp	1700
25.	Or/ 4-24	650350
26.	surgery.mp	660227
27.	treatment.mp	255751
28.	exp Health Services Accessibility/cl, og, st, sn, td, ut	16904
29.	exp Healthcare Disparities/	3400
30.	treatment disparities.mp	69
31.	exp "Delivery of Health Care"/	662295
32.	exp Primary Health Care/sn, td, ut	6839
33.	exp Drug Therapy/	921829
34.	Chemotherapy.mp or	236003
35.	Radiotherapy, Adjuvant/ or Radiotherapy/	45648
36.	Radiotherapy.mp	145755
37.	Accessibility.mp	56793
38.	Access.mp	123272
39.	Pattern$.mp	767175
40.	Palliative care/ or Patient care/ or Primary Health care/	83405
41.	Care.mp	1154474
42.	Investigation.mp	282065
43.	Exp "Quality of Health Care"/st, sn, td, ut	99809

44. Exp Patient Selection/ or exp Eligibility Determination/or exp Medicaid/	60372
45. Exp “Referral and Consultation”/ st, sn, td, ut	9243
46. Receipt.mp or exp “Patient Acceptance of Health Care”/	137892
47. Provision.mp	33164
48. Attendance.mp	11676
49. Or/26-48	5529748
50. 3 and 25 and 49	484
51. News.pt	130842
52. Comment.pt	438297
53. Letter.pt	712489
54. Review pt	1600963
55. Editorial.pt	274165
56. 50 not (or/51-55)	398

Table C3.2. EMBASE search strategy 05/05/11

Search Term	Number Retrieved
1. Exp lung cancer/ di, dm, dt, ep, rt, rh, su, th	71888
2. Exp LUNG CARCINOMA/ di, dm, dt, ep, rt, rh, su, th	43143
3. Exp lung non-Small-cell cancer/ di, dm, dt, ep, rt, rh, su, th	25650
4. exp small cell carcinoma/ di, dm, dt, ep, rt, rh, su, th	4284
5. Or/1-4	75298
6. Social Class/ or Socio-economic Factors/	105019
7. Socio-economic status.mp	5032
8. Education/ or exp Education, Continuing	264216
9. Socio-economic position.mp	254
10. Social factors.mp	5735
11. Income.mp	60981
12. Social Class.mp	24420
13. Education.mp	463082
14. Exp LOWEST INCOME GROUP/ or exp INCOME/	54541
15. Exp Poverty/	23046
16. Inequality.mp	7552
17. Inequalities.mp	6594
18. Exp Social Environment/	224660
19. Exp demography/	114434
20. Exp health disparity/	2317
21. Exp Health insurance/ or exp socioeconomics/ or exp Social status/	308865
22. Inequity.mp	1106
23. Equity.mp	5975
24. Exp CULTURAL DEPRIVATION/ or deprivation.mp	53312
25. Or/ 6-24	1301033
26. surgery.mp	1211103
27. treatment.mp	3334976
28. treatment disparities.mp	92

29. exp “Delivery of Health Care”/	1383093
30. exp Drug Therapy/	1219237
31. Chemotherapy.mp or	357346
32. Radiotherapy, Adjuvant/ or Radiotherapy/	68286
33. Radiotherapy.mp	202245
34. HEALTH CARE ACCESS/	27526
35. Access.mp	176386
36. Care.mp	1749819
37. Pattern$.mp	824237
38. Health service/ or health care policy/ or equity.mp or health care/ or health care delivery	332536
39. Quality.mp or HEALTH CARE QUALITY/	731294
40. Health care utilization/	28472
41. Provision.mp	39964
42. Attendance.mp	14211
43. Receipt.mp	7755
44. Terminal care/	18463
45. Or/26-44	7347896
46. 5 and 25 and 45	1708
47. Letter.pt	726344
48. Editorial.pt	370622
49. Note.pt	440574
50. Review.pt	1692350
51. 46 not (or/47-50)	1208
52. 51 and article.pt	1080

Appendix C4. Population over-lap and paper selection for inclusion

C4.1 UHCS papers

Three papers (198, 200, 201) all looked at the same single-year Scottish population and presented overlapping results. Two papers examined the same NYCRIS population (78, 199) but presented different results.

Four papers used Thames Cancer Registry data where two of the papers used overlapping data (202, 213) and one of the papers (158) used a subset population included in both other papers. The fourth paper (ref) used more recent data and did not overlap the other 3 papers.

Two papers by the same authors used LUCADA audit data, the first from 2004-2007 (153) and the second paper had a further year of audit data to 2008 (152). These were considered as one population and the paper with the larger population used where both were eligible for inclusion.

Three New Zealand papers all used the same study population (205, 206, 214).

The size of the UK populations examined ranged from 695 to over 60,000. The non-UK papers examined a smaller population size range – from 108 to 6449.

The majority of the papers used cancer registry data, some supplemented with data from medical records, and two used data from a lung cancer audit. Audit data includes only a subset of registry patients whose data has been entered into the audit.

Three UK papers obtained data from Hospital Episode Statistics [HES] and the three New Zealand papers included only patients who were admitted to secondary care. Papers that used only HES/hospital data were able to look at inequalities in care only for those admitted to hospital, not the entire registry population.

C4.2 Non-UHCS studies

There is also overlap within the SEER dataset so again only substantially non-overlapping studies were included in the final meta-analyses. Alternative analyses including all eligible studies were also run, as well as analyses including partially overlapping studies but not those that were fully a subset of another.

C4.3 Choosing the most suitable studies for inclusion in meta-analysis

Problems did arise where two studies used the same population, or a subset of a population, but found slightly different results. Quality score was used as the initial selection factor for the most appropriate study to choose for inclusion in the meta-analysis.

In some cases the smaller regional analyses were of better quality as they included stage and histology, whereas the analysis of the national population did not. For example the Berglund (2012) paper looked at patients diagnosed between 2006 and 2008 in the Thames Cancer Registry region (157). However, Riaz (2012) looked at England-wide data diagnosed between 2004 and 2006 (161) and so there is likely to be some overlap between these populations for 2006. So although these are clearly different populations they are not entirely unique populations. The Berglund study is smaller (1826 in the surgery population) compared to Riaz (77,349) but Berglund includes stage and co-morbidity and so is the better quality study.

The two Rich [2011] studies (152, 153) include England-wide data for 2004-2007 (24,175 patients) and 2004-2008 (34,436 patients) respectively, obtained from the LUCADA audit and so these two had clearly overlapping populations where it would only be suitable to include one in the meta-analysis. But again some of the same patients are likely to be included here that are also found in the Riaz (161) and Berglund (157) studies, although different sources have been used [LUCADA rather than Registry data]. Therefore, although the overlap may be small, strictly speaking only one of these four studies should be included in the final meta-analysis. The quality score was therefore used to decide this. Berglund (157) was the smallest study but the best quality.

Sensitivity analyses including all the over-lapping populations meant that three large, reasonable quality studies were still able to supply data to the meta-analyses. Further analyses were then run where only non-overlapping populations were included and, where it was not clear which was the best of the over-lapping populations to include, multiple analyses were run using different study combinations, to see if this made any difference to the overall outcome. It was therefore possible to examine whether it might be better to choose a slightly less-good quality study that contained more data,

for example, the larger Rich paper (152) as it contained stage and co-morbidity but did not capture everyone diagnosed within the timescale, or the Riaz paper (161) which had better population capture but did not include important confounders such as stage and co-morbidity.

Appendix C5: Quality Score

Quality Score	Characteristics of studies
6	Multi-variable analysis. Population-based sample. Good internal validity/reporting/confounding
5	Multi-variable analysis. Selective population. Good internal validity/reporting/confounding
4	Multi-variable analysis. Population-based sample. Some problems with internal validity/reporting/confounding (eg good internal validity/reporting but stage not included OR less good internal validity/reporting and stage included)
3	Multi-variable analysis. Selective population. Some issues with internal validity/reporting/confounding (eg good internal validity/reporting but stage not included OR less good internal validity/reporting and stage included)
2	Univariable analysis. Good internal validity/reporting OR multivariable analysis but only univariable results reported or no CIs/ different comparator/ stratified by other variable
1	Univariable analysis. Poor internal validity/reporting OR multivariable analysis but results for SEP not shown or errors in data

Quality checklist used to derive quality scores

Screening questions:

Does the study conduct **multivariable** analysis and report **adjusted** odds ratios/rates?

Yes – consider for meta-analysis

No – consider for narrative review

What **population** is included?

a. Population-based sample: eg total local or national lung cancer population from a cancer Registry
b. Selective population: eg. hospital population from Hospital Episode Statistics (HES) data or similar, or from Registry linked to Medicare records (USA) or incomplete audit data

Section 1: Internal validity

1. Appropriate, valid and reliable measure of SEP is used (e.g. IMD, Carstairs, Townsend, similar local index, income, poverty level, education)
    a. Yes - individual standard measure used 5
    b. Yes - area-based standard measure used 3
    c. Standard measure used but presented as average for PCT/health authority 1
    d. Non-standard measure used/ measure not reported 0
2. SEP categorised as
    a. Continuous/Deciles 5
    b. Quintiles/ Quartiles 3
    c. Tertiles/Dichotimised 1
    d. Unknown/ not reported 0
3. SEP expressed as an OR to
    a. Two decimal places 5

b. One decimal place 3
c. Whole number/ expressed as rate 1
d. unknown/not reported 0

4. Outcome measures are valid and reliable
    a. Yes - care/ treatment details obtained from Registry, HES or similar system 3
    b. Yes - care/treatment details obtained from audit or hospital records 3
    c. Care treatment details obtained from survey/questionnaire/other 1
    d. No/unknown/not reported 0

Good: 14-18 OK: 13-11 Poor: 0-10

Section 2: External validity

1. Population
    a. Study uses multiple Registry or national population(s) or similar 3
    b. Study uses regional population from Registry or HES or similar 2
    c. Study uses only small subset of population (some health boards/PCTs/areas) 1
    d. Study uses small, random sample from Registry or hospital data /other 1
    e. Population not stated 0
2. Population date and time period
    a. Multiple years of diagnosis, some post-2000 3
    b. Multiple years of diagnosis, all pre-2000 2
    c. Single year of diagnosis, post -2000 2
    d. Single year of diagnosis, pre-2000 1

Good: 4-6 Poor: 0-3

Section 3: Reporting of Study

1. Outcome measures are clearly defined/reported
    a. Yes 1
    b. No 0
2. Outcome measure reported
    a. Rates/odds of treatment compared with no treatment 2
    b. Rates/odds of NOT receiving treatment compared to receiving treatment 2
    c. Rates/odds of treatment compared with other care 1
    d. Rates/odds of treatment stratified by other variable (sex, race etc) 1
    e. Results presented in some other way 0
3. Number initially eligible/ number excluded reported
    a. Eligible/excluded/included all reported or able to be calculated 2
    b. Number included reported only 1
    c. Numbers not reported 0
4. Inclusion/ exclusion criteria detailed
    a. Yes 1
    b. No 0

5. Numbers receiving treatment
    a. Numerator and denominator populations clearly documented 2
    b. Numbers calculable from details given but not clearly specified 1
    c. Numbers not specified 0
    d. Numbers do not add up correctly and need to be checked with authors 0
6. Other variables that are significant in analysis reported
    a. Yes 2
    b. Yes, but results for only some presented 1
    c. No 0
7. Death Certificate Only (DCO) excluded
    a. Yes 1
    b. Not applicable (if using HES type data) 1
    c. No/ not reported 0
8. Confidence interval reported
    a. Yes 1
    b. No 0
9. P value reported
    a. Overall p value/ p for trend 2
    b. Individual p values 1
    c. Not reported 0

Good: 11-14 OK: 7-10 Poor: 0-6

Section 4: Confounding

1. Multivariable analysis - other important confounders included
    a. Age and sex 3
    b. Age or Sex 2
    c. Univariable analysis only reported 1
    d. Descriptive only/ no analysis 0
2. Results stratified by stage
    a. Yes, and only eligible- stage patients used for denominator 3
    b. Yes, but all-stage patients used for denominator 2
    c. No, but stage included as a confounder 2
    d. No 0
3. Results stratified by histology
    a. Yes, and only histologically-verified cases included 3
    b. Yes, but clinically diagnosed and histologically-unknown cases included 2
    c. No, but histology included as a confounder 2
    d. No 0
4. Other relevant confounders included
    a. Co-morbidity/ performance status 2
    b. Trust/ health board/ hospital/area 1
    c. No 0

Good: 7-11 (must include age, sex, stage and histology)

OK: 3-5 (must include age, sex)Poor: 0-2 (univariable analysis)

Appendix C6. Assessment of existing quality assessment tools

The Cochrane tool for assessment of risk of bias is only suitable for randomised controlled trials as the tool examines aspects of studies such as randomisation and blinding which are not relevant in cohort studies. However, the measures of the four different types of biases identified [selection, performance, attrition and detection] can be adapted for other types of studies. For example RCTs use randomisation to prevent selection bias but in cohort studies controlling for confounders can be considered instead (190). Measurement of exposure in cohort studies rather than blinding of participants/investigators can be used to check for performance bias. Completeness of follow-up to assess attrition bias and blinded outcome assessment for detection bias can be examined for cohort studies as they can for RCTs (190).

Other tools used by Cochrane Review Groups include the Jadad scale (191) which again is only suitable for RCTs. The Moncrief scale includes items on external validity and reporting of statistical analysis which are not necessarily measures of bias (191).

The Newcastle-Ottawa scale is recommended by the Musculoskeletal Cochrane Group (191). This scale has been developed for assessing the quality of non-randomised studies and so is potentially suitable for cohort studies. Studies are assessed on selection, comparability and outcome and so this does appear to be more of a measure of the internal validity of a study than some of the other scales examined. The scale is divided into: Selection of the cohorts [4 items]; Comparability of the cohorts [1 item]; and Assessment of outcome [3 items]. 'High quality' outcomes are identified with a star, with a maximum of 1 star per item in the selection category and 2 stars per item in the comparability category [but the number of stars in the outcome category is not stated]. These star charts can then be presented alongside the meta-analysis. Although published Cochrane reviews do utilise scales and many of their Review Groups recommend them (191) their validity has not been demonstrated in empirical research. Therefore the validity of the scale is unclear and the definition of 'good' and 'poor' scores appears somewhat subjective. Also, the scale does not appear to have been published as, after online searching, only a power point presentation was available.

SIGN, the Scottish Intercollegiate Guidelines Network has a methodology checklist for cohort studies (192). This examines internal validity under the following headings: selection of subjects, confounding, statistical analysis. Each criterion [for example: 'The outcomes are clearly defined'] is assessed as: well covered, adequately addressed, poorly addressed, not addressed, not reported, not applicable. In the overall assessment of the study a score of ++, + or – is given for how well has the study minimised the risk of bias or confounding and a judgment made on applicability and certainty that the overall effect is due to the study intervention.

A more extensive checklist than SIGN is utilised by the Effective Public Health Practice Project [EPHPP] Quality Assessment Tool for Quantitative Studies in Canada (193), which looks at selection bias, study design, confounders, blinding, data collection methods, withdrawals and drop-outs, intervention integrity and analyses. Each section is rated as strong, moderate or weak. Not all of these categories are relevant for the type of studies included in this review as all are cohort studies, no blinding takes place and as participants are not actively recruited they cannot drop out, but parts of it could be adapted and utilised.

The STROBE [Strengthening the Reporting of Observational Studies in Epidemiology] guidelines (194) contain a checklist of 22 items that should be included in cohort studies. The quality of reporting on the following criteria can be assessed: study design, size, setting, dates, data sources, eligibility criteria, number of participants potentially eligible, number actually included, number analysed, missing/incomplete data reported, variables included [in terms of outcome, exposure, predictors, confounders], type of statistical analysis carried out, unadjusted and adjusted estimates reported, precision [confidence intervals], significance [p values] given, limitations of the study, potential bias addressed, external validity of results, funding source.

Although the STROBE guidelines are a checklist measure of good reporting rather than 'an instrument to evaluate the quality of observational research' (194), a number of other lung cancer systematic reviews use some of the above items in their scales for quality ascertainment (185, 188). However, just because something is not reported

does not necessarily mean it was not done. However, in order to determine this it may be necessary to contact the authors of the study.

Conclusion

Following review of the potential tools identified above, criteria adapted from SIGN, EPHPP and STROBE guidelines were used to develop a quality assessment tool for this systematic review.

Appendix C7: Sensitivity meta-analyses

Figure C7.1. Meta-analysis of odds of receipt of surgery in low (most deprived) versus high (least deprived) SEP. (over-lapping populations; n=16)

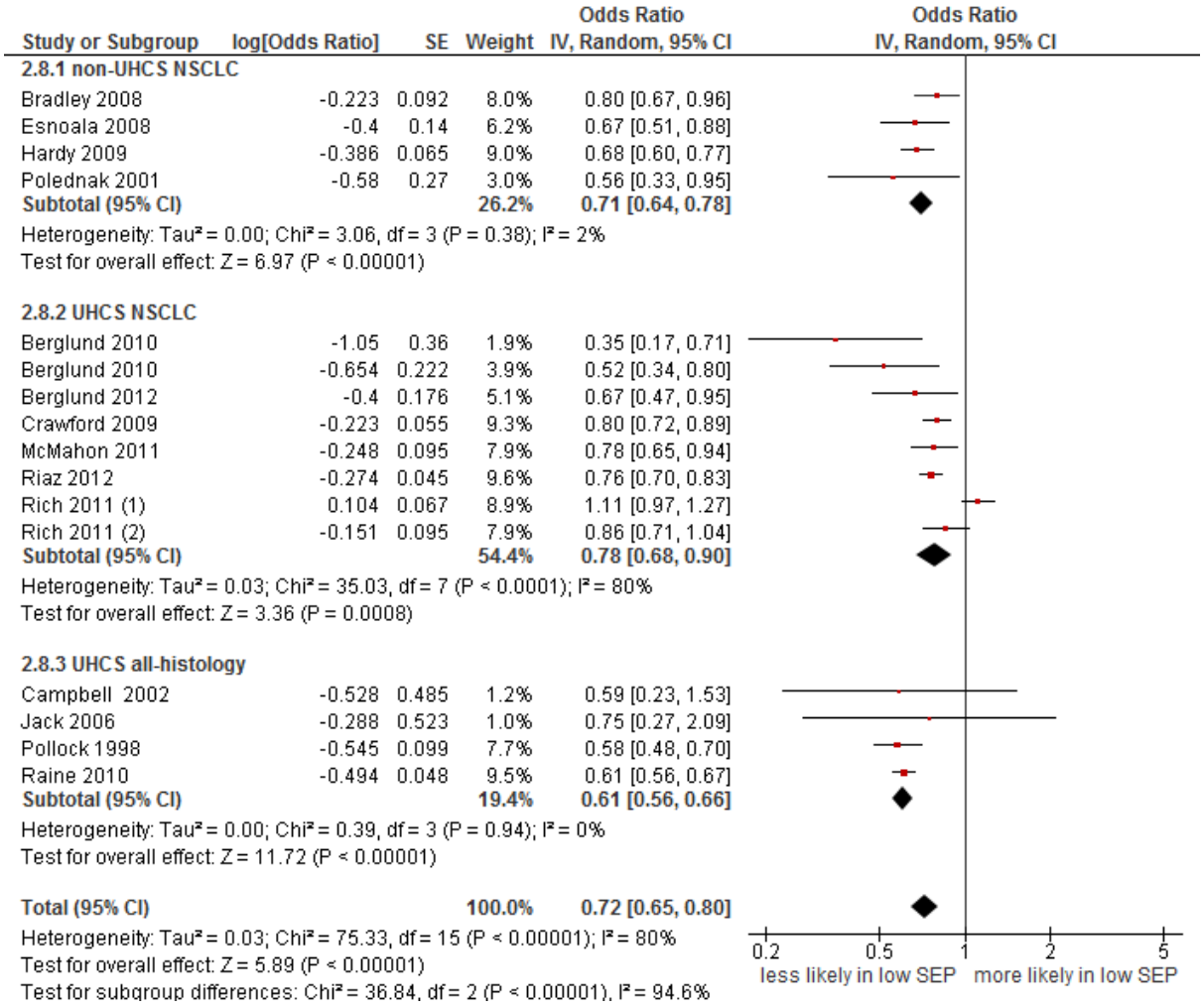


Figure C7.2. Meta-analysis of odds of receipt of surgery for NSCLC in low (most deprived) versus high (least deprived) SEP. (non-overlapping populations; n=8)

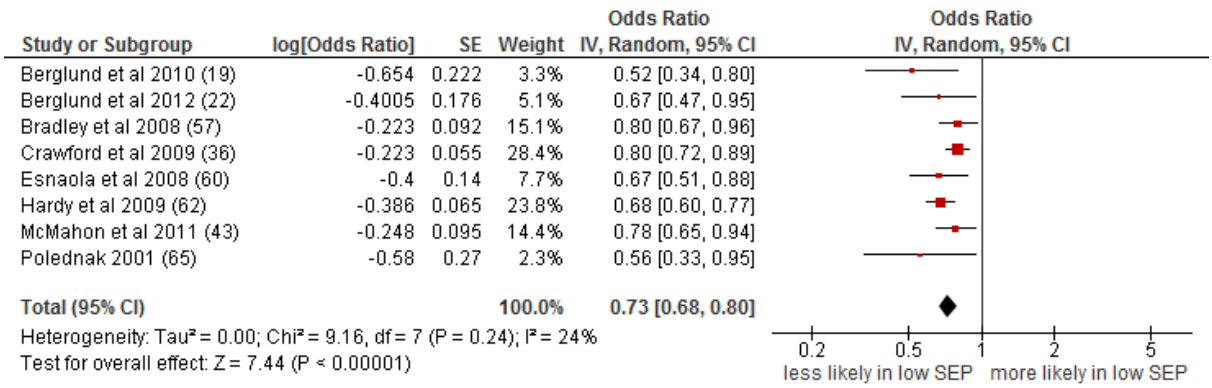


Figure C7.3. Meta-analysis of odds of receipt of chemotherapy in low (most deprived) versus high (least deprived) SEP (over-lapping populations; n=10).

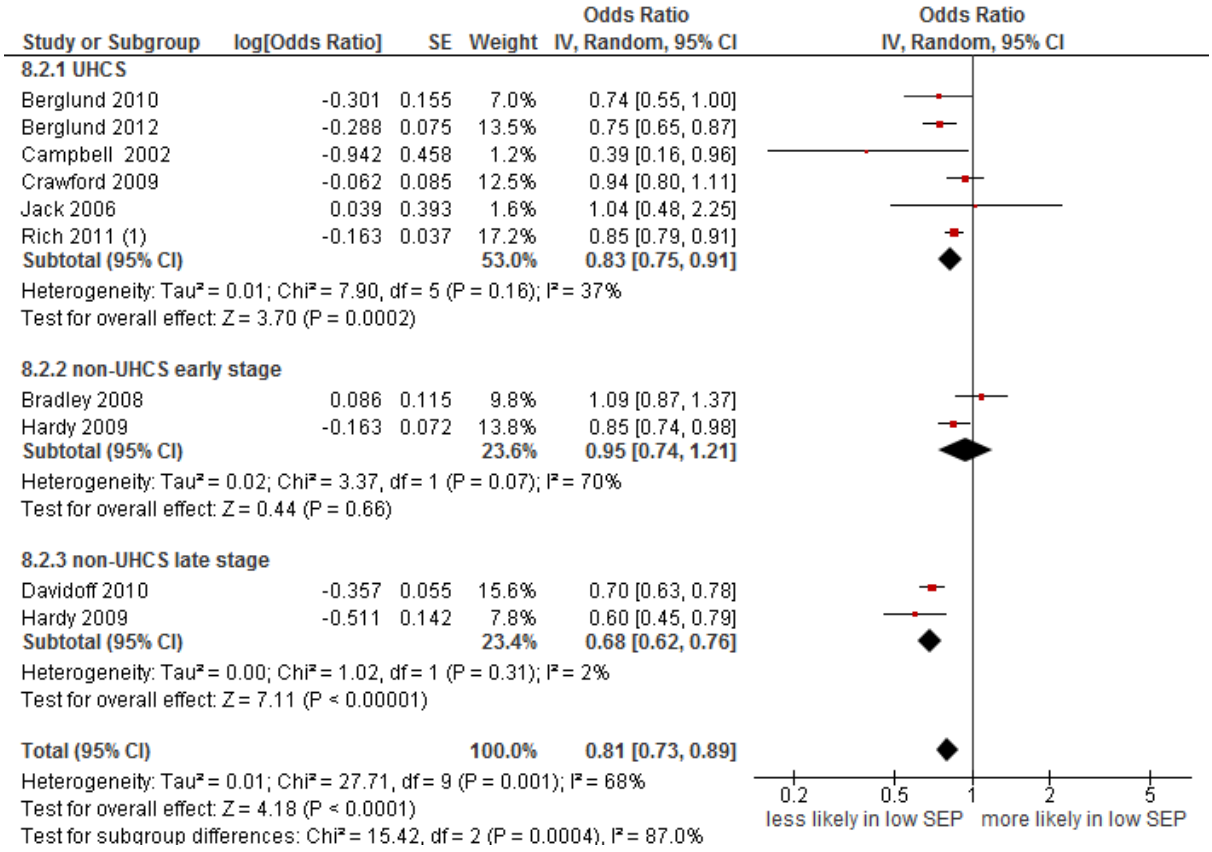


Figure C7.4. Meta-analysis of odds of receipt of radiotherapy in low (most deprived) versus high (least deprived) SEP (overlapping populations; n=9).

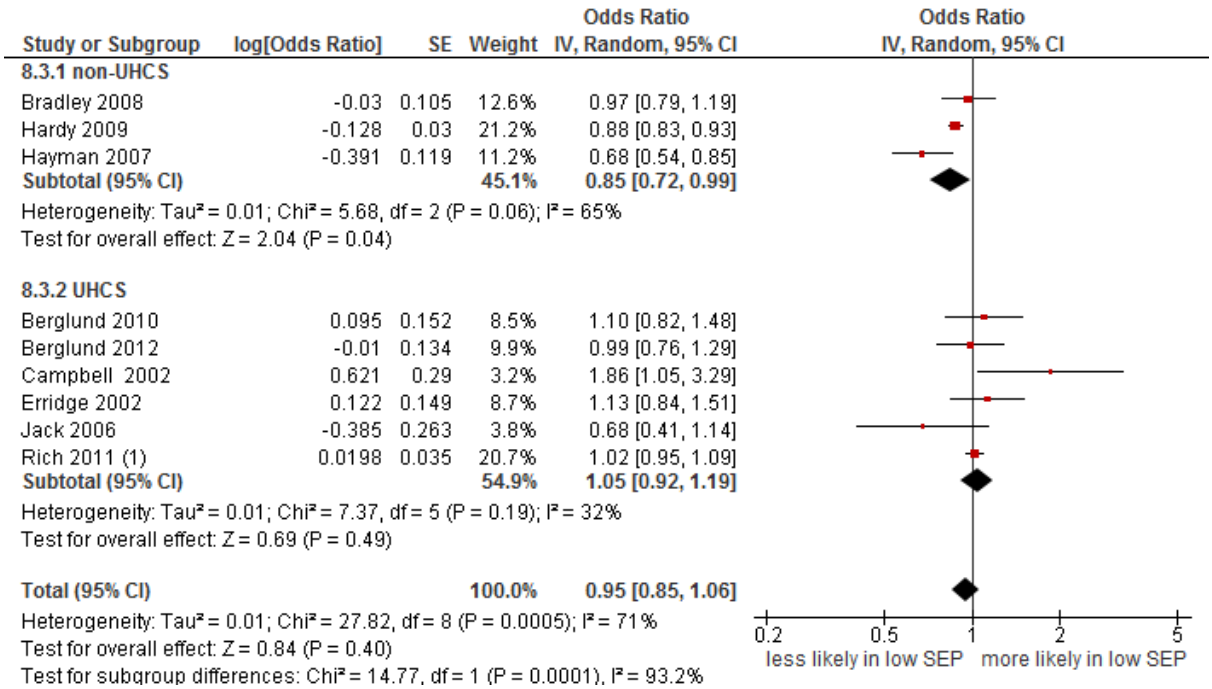


Figure C7.5. Meta-analysis of odds of receipt of any type of treatment in low (most deprived) versus high (least deprived) SEP (overlapping populations; n=35).

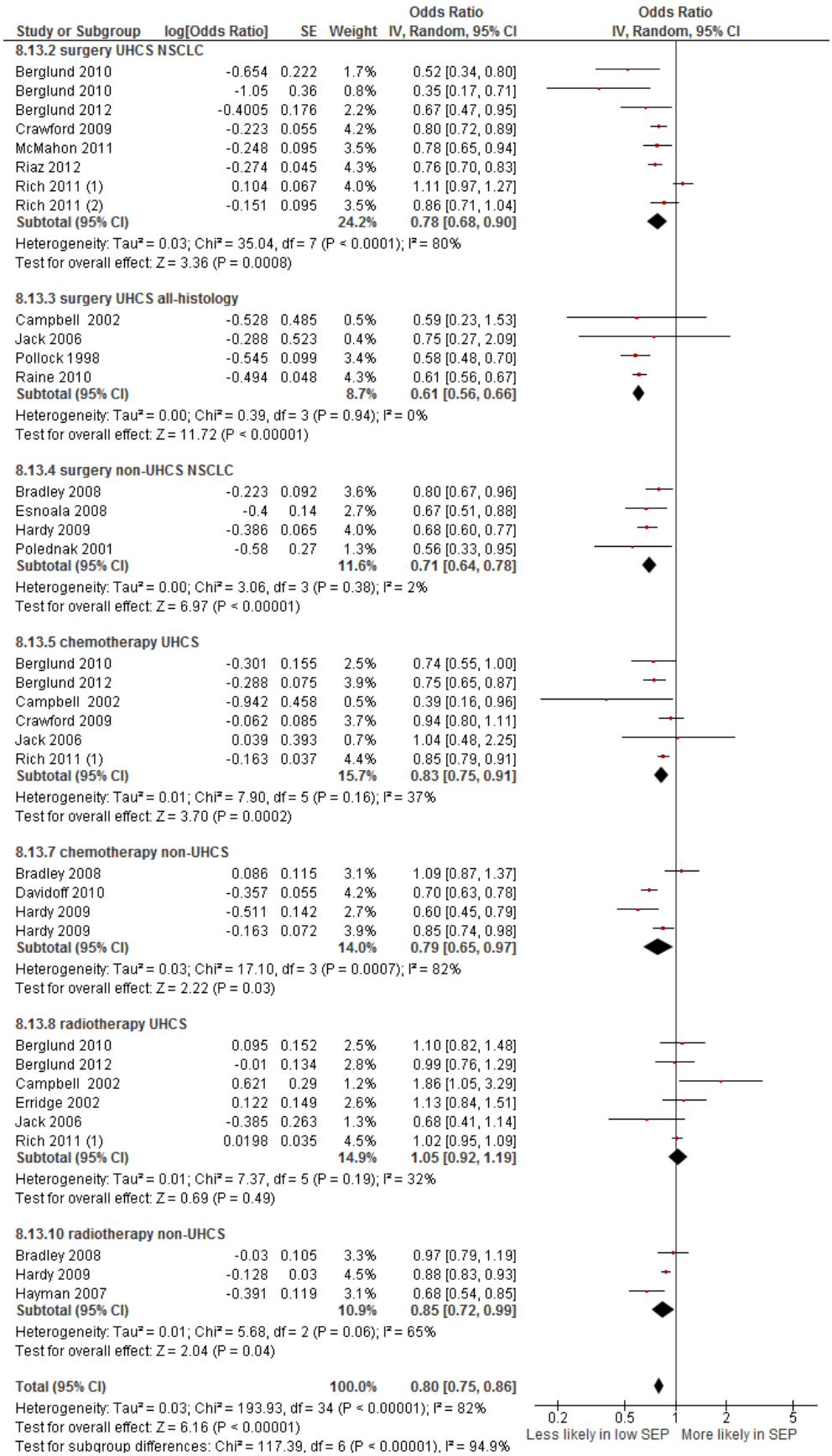
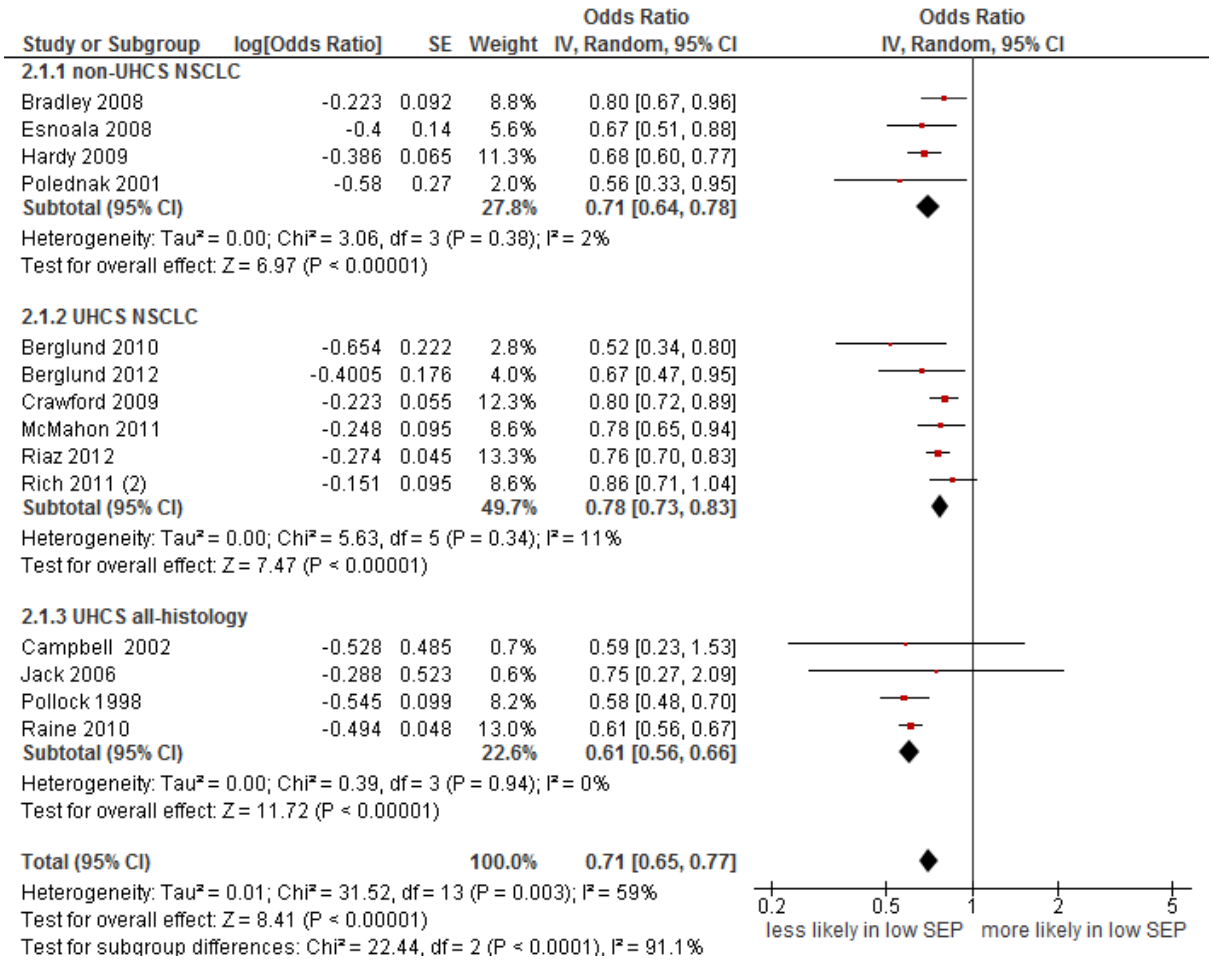


Figure C7.6. Meta-analysis of odds of receipt of surgery in low versus high SEP. (partially-overlapping populations, n=14)



14.4 Appendix D: Supplementary tables for chapters 11 and 12

Table D.1. Odds of FHA within 2 weeks from GP referral (for those with FHA within 1 year of GP ref) 1999-2005

Variables	FHA within 1 year	FHA within 2 weeks		Univariable analysis (n=16,649)				Multivariable analysis[1] (n=16,649, R^2=3.42)			
	N	N	%	OR	95% CI		P	OR	95% CI		P
IMD	**16,649**	**12,241**	**73.5**				**0.28**				**0.16**
1	1,815	1,357	74.8	1.00				1.00			
2	2,400	1,792	74.7	0.99	0.86	1.14	0.94	0.96	0.83	1.10	0.55
3	2,796	2,043	73.1	0.92	0.80	1.05	0.20	0.89	0.77	1.02	0.09
4	3,847	2,793	72.6	0.89	0.79	1.02	0.09	0.86	0.76	0.98	0.03
5	5,791	4,256	73.5	0.94	0.83	1.06	0.28	0.90	0.80	1.02	0.10
Age Range	**16,649**	**12,241**	**73.5**				**<0.001**				**<0.001**
<60	2,561	1,970	76.9	1.00				1.00			
60-69	4,707	3,517	74.7	0.89	0.79	0.99	0.04	0.92	0.82	1.03	0.14
70-79	6,635	4,834	72.9	0.81	0.72	0.90	<0.001	0.86	0.77	0.96	0.01
80+	2,746	1,920	69.9	0.70	0.62	0.79	<0.001	0.79	0.69	0.89	<0.001
Sex	**16,649**	**12,241**	**73.5**				**0.76**				**0.59**
Female	6,909	5,071	73.4	1.00				1.00			
Male	9,740	7,170	73.6	1.01	0.94	1.08	0.76	1.02	0.95	1.10	0.59
Histology	**16,649**	**12,241**	**73.5**				**<0.001**				**<0.001**
NSCLC	9,865	7,236	73.4	1.00				1.00			
SCLC	2,341	1,905	81.4	1.59	1.42	1.78	<0.001	1.59	1.42	1.79	<0.001
Other	4,443	3,100	69.8	0.84	0.78	0.91	<0.001	0.88	0.81	0.96	<0.001
Year of Diagnosis	**16,649**	**12,241**	**73.5**				**<0.001**				**<0.001**
1999	2,345	1,608	68.6	1.00				1.00			
2000	2,355	1,714	72.8	1.59	1.41	1.79	<0.001	1.24	1.10	1.41	<0.001
2001	2,404	1,860	77.4	1.95	1.72	2.20	<0.001	1.60	1.40	1.82	<0.001
2002	2,379	1,865	78.4	2.49	2.20	2.82	<0.001	1.69	1.48	1.93	<0.001
2003	2,422	1,954	80.7	2.64	2.33	3.00	<0.001	1.96	1.71	2.24	<0.001
2004	2,350	1,855	78.9	3.04	2.67	3.46	<0.001	1.76	1.54	2.01	<0.001
2005	2,394	1,385	57.9	2.73	2.40	3.10	<0.001	0.64	0.57	0.72	<0.001
Co-morbidity score	**16,649**	**12,241**	**73.5**				**<0.001**				**<0.001**
0	2,681	1,888	70.4	1.00				1.00			
1-2	1,151	763	66.3	0.83	0.71	0.96	0.01	0.87	0.75	1.01	0.07
3+	175	110	62.9	0.71	0.52	0.98	0.04	0.76	0.55	1.06	0.10
CCM missing	11,178	8,438	75.5	1.29	1.18	1.42	<0.001	1.29	1.18	1.42	<0.001
No HES link	1,464	1,042	71.2	1.04	0.90	1.19	0.61	1.19	1.03	1.38	0.02

[1] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score

Table D.2. Odds of receiving any treatment within 31 days of diagnosis (for those treated within 1 year of diagnosis) 1999-2005

	Treated	Treated within 31 days		Univariable analysis (n=19,510)				Multivariable analysis[1] (n=19,510, R^2=10.50)			
	N	N	%	OR	95% CI		P	OR	95% CI		P
IMD	**19,510**	**8,457**	**43.4**				**0.004**				**0.001**
1	2,208	1,036	46.9	1.00				1.00			
2	2,828	1,247	44.1	0.89	0.80	1.00	0.05	0.91	0.81	1.03	0.12
3	3,182	1,371	43.1	0.86	0.77	0.96	0.005	0.88	0.78	0.98	0.03
4	4,405	1,866	42.4	0.83	0.75	0.92	<0.001	0.83	0.74	0.92	0.001
5	6,887	2,937	42.7	0.84	0.76	0.93	<0.001	0.82	0.74	0.91	<0.001
Age Range	**19,510**	**8,457**	**43.4**				**<0.001**				**<0.001**
<60	4,073	2,085	51.2	1.00				1.00			
60-69	6,389	2,886	45.2	0.79	0.73	0.85	<0.001	0.83	0.76	0.90	<0.001
70-79	7,274	2,887	39.7	0.63	0.58	0.68	<0.001	0.77	0.71	0.84	<0.001
80+	1,774	599	33.8	0.49	0.43	0.55	<0.001	0.68	0.60	0.78	<0.001
Sex	**19,510**	**8,457**	**43.4**				**<0.001**				**0.58**
Female	8,060	3,641	45.2	1.00				1.00			
Male	11,450	4,816	42.1	0.88	0.83	0.93	<0.001	0.98	0.92	1.05	0.58
Histology	**19,510**	**8,457**	**43.4**				**<0.001**				**<0.001**
NSCLC	12,551	4,269	34.0	1.00				1.00			
SCLC	3,705	2,867	77.4	6.64	6.09	7.23	<0.001	4.76	4.32	5.25	<0.001
Other	3,254	1,321	40.6	1.33	1.22	1.43	<0.001	1.41	1.30	1.53	<0.001
Co-morbidity score	**19,510**	**8,457**	**43.4**				**<0.001**				**0.28**
0	3,464	1,469	42.4	1.00				1.00			
1-2	1,790	726	40.6	0.93	0.83	1.04	0.20	0.98	0.87	1.12	0.81
3+	273	110	40.3	0.92	0.71	1.18	0.50	1.01	0.77	1.32	0.96
CCM missing	13,210	5,866	44.4	1.08	1.01	1.17	0.04	1.06	0.97	1.15	0.18
No HES link	773	286	37.0	0.80	0.68	0.94	0.006	1.16	0.98	1.38	0.08
Diagnosis year	**19,510**	**8,457**	**43.4**				**0.10**				**0.01**
1999	2,844	1,246	43.8	1.00				1.00			
2000	2,901	1,225	42.2	0.94	0.84	1.04	0.23	0.87	0.77	0.97	0.01
2001	2,776	1,200	43.2	0.98	0.88	1.09	0.66	0.96	0.86	1.08	0.49
2002	2,766	1,155	41.8	0.92	0.83	1.02	0.12	0.86	0.76	0.96	0.009
2003	2,705	1,230	45.5	1.07	0.96	1.19	0.21	1.00	0.89	1.12	1.00
2004	2,701	1,156	42.8	0.96	0.86	1.07	0.45	0.86	0.77	0.97	0.01
2005	2,817	1,245	44.2	1.02	0.91	1.13	0.77	0.95	0.85	1.07	0.39
GP referral	**19,510**	**8,457**	**43.4**				**<0.001**				**<0.001**
No GP referral date	8,645	4,117	47.6	1.00				1.00			
<=14 days to FHA	8,107	3,424	42.2	0.80	0.76	0.85	<0.001	0.79	0.73	0.84	<0.001
>14 days to FHA	2,758	916	33.2	0.55	0.50	0.60	<0.001	0.59	0.54	0.65	<0.001
Ist treatment	**19,510**	**8,457**	**43.4**				<0.001				**<0.001**
Chemotherapy	6,949	4,248	61.1	1.00				1.00			
Surgery	3,430	1,330	38.8	0.40	0.37	0.44	<0.001	0.76	0.69	0.83	<0.0011
Radiotherapy	9,131	2,879	31.5	0.29	0.27	0.31	<0.001	0.53	0.49	0.58	<0.001

[1] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, GP referral, first treatment

Table D.3. Odds of receiving any treatment within 62 days of GP referral (for those with FHA within 1 year of referral, diagnosis within 1 year of FHA and treated within 1 year of diagnosis) 1999-2005

	Treated	Treated within 62 days		Univariable analysis (n=10,844)				Multivariable analysis[1] (n=10,844, R^2=9.71)			
	N	N	%	OR	95% CI		P	OR	95% CI		P
IMD	**10,844**	**5,326**	**49.1**				**0.005**				**0.0002**
1	1,220	646	53.0	1.00				1.00			
2	1,628	825	50.7	0.91	0.79	1.06	0.23	0.92	0.79	1.08	0.32
3	1,796	901	50.2	0.89	0.77	1.03	0.13	0.89	0.76	1.04	0.16
4	2,476	1,173	47.4	0.80	0.70	0.92	0.001	0.78	0.67	0.90	0.001
5	3,724	1,781	47.8	0.81	0.72	0.93	0.002	0.77	0.67	0.88	<0.001
Age Range	**10,844**	**5,326**	**49.1**				**<0.001**				**<0.001**
<60	2,146	1,233	57.5	1.00				1.00			
60-69	3,616	1,843	51.0	0.77	0.69	0.86	<0.001	0.82	0.73	0.92	0.001
70-79	4,054	1,826	45.0	0.61	0.55	0.67	<0.001	0.74	0.66	0.83	<0.001
80+	1,028	424	41.3	0.52	0.45	0.60	<0.001	0.70	0.59	0.82	<0.001
Sex	**10,844**	**5,326**	**49.1**				**0.38**				**0.21**
Female	4,436	2,201	49.6	1.00				1.00			
Male	6,408	3,125	48.8	0.97	0.90	1.04	0.38	1.05	0.97	1.14	0.21
Histology	**10,844**	**5,326**	**49.1**				**<0.001**				**<0.001**
NSCLC	7,290	3,091	42.4	1.00				1.00			
SCLC	1,911	1,550	81.1	5.83	5.15	6.60	<0.001	3.66	3.19	4.20	<0.001
Other	1,643	685	41.7	0.97	0.87	1.08	0.60	1.04	0.93	1.16	0.54
Co-morbidity score	**10,844**	**5,326**	**49.1**				**<0.001**				**<0.001**
0	1,824	799	43.8	1.00				1.00			
1-2	729	316	43.4	0.98	0.83	1.17	0.83	1.05	0.87	1.26	0.61
3+	97	33	34.0	0.66	0.43	1.02	0.06	0.73	0.46	1.15	0.17
CCM missing	7,763	3,990	51.4	1.36	1.22	1.50	<0.001	1.32	1.18	1.47	<0.001
No HES link	431	188	43.6	0.99	0.80	1.23	0.94	1.38	1.11	1.73	0.004
Diagnosis year	**10,844**	**5,326**	**49.1**				**0.01**				**0.04**
1999	1,541	745	48.4	1.00				1.00			
2000	1,530	697	45.6	0.89	0.78	1.03	0.12	0.86	0.74	1.00	0.05
2001	1,530	767	50.1	1.07	0.93	1.24	0.32	1.07	0.92	1.25	0.37
2002	1,552	747	48.1	0.99	0.86	1.14	0.91	0.92	0.79	1.07	0.28
2003	1,581	778	49.2	1.04	0.90	1.19	0.63	0.96	0.82	1.12	0.60
2004	1,534	766	49.9	1.07	0.93	1.23	0.38	0.96	0.82	1.12	0.58
2005	1,576	826	52.4	1.18	1.02	1.35	0.02	1.08	0.93	1.26	0.33
1st treatment	**10,844**	**5,326**	**49.1**				**<0.001**				**<0.001**
Chemotherapy	3,985	2,732	68.6	1.00				1.00			
Surgery	1,882	619	32.9	0.22	0.20	0.25	<0.001	0.36	0.32	0.41	<0.001
Radiotherapy	4,977	1,975	39.7	0.30	0.28	0.33	<0.001	0.50	0.45	0.56	<0.001

[1] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, first treatment

Table D.4. Hazard ratio of early first hospital appointment from GP referral (for those referred within 1 year) in 2006-2010 cohort with stage recorded

		Median time to FHA (days)		Univariable analysis (n=5100)				Multivariable analysis (n=5100)			
	N	N	IQR	HR	95% CI		P	HR	95% CI		P
IMD	**5100**	**9**	**4-14**				**0.28**				**0.16**
1	594	8	4-14	1.00				1.00			
2	705	9	5-14	0.93	0.84	1.04	0.21	0.95	0.85	1.06	0.32
3	839	9	5-15	0.90	0.81	1.00	0.05	0.89	0.80	0.99	0.03
4	1198	9	5-14	0.91	0.83	1.01	0.07	0.90	0.81	0.99	0.03
5	1764	9	4-15	0.95	0.87	1.04	0.27	0.93	0.85	1.02	0.13
Age Range	**5100**	**9**	**4-14**				**0.34**				
<60	682	9	4-14	1.00				1.00			
60-69	1490	9	5-14	1.01	0.93	1.11	0.75	1.00	0.91	1.10	1.00
70-79	1876	9	5-15	0.95	0.87	1.04	0.30	0.93	0.85	1.02	0.11
80+	1052	8	3-15	0.99	0.90	1.09	0.79	0.91	0.82	1.01	0.07
Sex	**5100**	**9**	**4-14**				**0.18**				**0.46**
female	2297	9	4-14	1.00				1.00			
male	2803	9	5-15	0.96	0.91	1.02	0.18	0.98	0.93	1.04	0.46
Histology	**5100**	**9**	**4-14**				**<0.001**				
NSCLC	3518	9	6-15	1.00				1.00			
SCLC	386	8	4-13	1.23	1.11	1.37	0.00	1.10	0.99	1.22	0.09
Other	1196	8	1-14	1.14	1.07	1.22	0.00	1.06	0.99	1.14	0.11
Year of Diagnosis	**5100**	**9**	**4-14**				**<0.001**				**<0.001**
2006	395	14	9-23	1.00				1.00			
2007	473	14	8-22	1.03	0.90	1.17	0.70	1.00	0.88	1.15	0.98
2008	968	7.5	4-12	1.70	1.51	1.92	<0.001	1.64	1.46	1.85	<0.001
2009	1492	8	3-13	1.68	1.50	1.87	<0.001	1.78	1.56	2.04	<0.001
2010	1772	8	3-14	1.53	1.37	1.71	<0.001	1.59	1.38	1.82	<0.001
Co-morbidity score	**5100**	**9**	**4-14**				**0.005**				
0	618	9	5-15	1.00				1.00			
1-2	508	8	3-18	0.93	0.82	1.07	0.31	0.93	0.83	1.05	0.26
3+	110	8	2-15	1.05	0.88	1.25	0.59	0.88	0.72	1.08	0.24
CCM missing	1259	10	6-16	1.03	0.84	1.26	0.77	1.19	1.06	1.32	0.002
No HES link	2605	8	3-14	1.11	1.02	1.21	0.01	1.02	0.92	1.12	0.75
Stage	**5100**	**9**	**4-14**				**<0.001**				**<0.001**
I	773	11	7-20	1.00				1.00			
II	399	11	5-16	1.20	1.06	1.35	0.003	1.20	1.06	1.36	0.004
III	1578	9	6-15	1.26	1.16	1.38	<0.001	1.23	1.12	1.34	<0.001
IV	2350	8	3-14	1.45	1.33	1.57	<0.001	1.35	1.24	1.47	<0.001
Performance Status	**5100**	**9**	**4-14**				**<0.001**				
0	1111	11	6-15	1.00				1.00			
1-2	2634	9	5-15	1.05	0.97	1.12	0.22	1.02	0.95	1.10	0.56
3-4	1016	6	0-13	1.39	1.28	1.51	<0.001	1.32	1.20	1.45	<0.001
Missing/ unknown	339	11	7-18	0.93	0.82	1.05	0.24	1.01	0.89	1.15	0.84

[1] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, stage, PS

Table D.5. Likelihood of still being alive 2 years after diagnosis, by selected patient, tumour and system factors for those diagnosed between 1999 and 2005 (DCO cases excluded)

variable	Adjusted – selected[1] (n=36,477, R^2=5.80)				Adjusted – selected[2] (n=36,477, R^2=24.60)			
	OR	95% CI		P	OR	95% CI		P
Deprivation quintile				**0.003**				**0.64**
1 (least deprived)	1.00				1.00			
2	0.97	0.86	1.10	0.68	1.02	0.89	1.18	0.74
3	0.90	0.80	1.01	0.08	1.01	0.88	1.15	0.94
4	0.86	0.77	0.96	0.01	0.98	0.86	1.12	0.80
5 (most deprived)	0.84	0.76	0.94	0.002	1.06	0.94	1.20	0.38
Age group				**<0.001**				**0.15**
<60	1.00				1.00			
60-69	0.85	0.78	0.93	<0.001	0.99	0.89	1.09	0.78
70-79	0.61	0.56	0.66	<0.001	0.95	0.86	1.06	0.35
80+	0.32	0.29	0.36	<0.001	0.86	0.74	0.99	0.03
Sex				**<0.001**				**<0.001**
Female	1.00				1.00			
Male	0.74	0.69	0.78	<0.001	0.71	0.66	0.76	<0.001
Histology				**<0.001**				**<0.001**
NSCLC	1.00				1.00			
SCLC	0.37	0.33	0.41	<0.001	0.59	0.52	0.67	<0.001
Other	0.59	0.55	0.64	<0.001	1.05	0.96	1.15	0.28
Year of Diagnosis				**<0.001**				**<0.001**
1999	1.00				1.00			
2000	1.17	1.04	1.32	0.009	1.17	1.02	1.34	0.03
2001	1.12	0.99	1.26	0.07	1.17	1.02	1.35	0.02
2002	1.15	1.02	1.29	0.03	1.21	1.05	1.39	0.01
2003	1.22	1.08	1.37	0.001	1.30	1.13	1.49	<0.001
2004	1.20	1.07	1.36	0.002	1.32	1.15	1.52	<0.001
2005	1.18	1.05	1.33	0.01	1.26	1.10	1.44	<0.001
Co-morbidity score				**<0.001**				**0.18**
0	1.00				1.00			
1-2	0.85	0.75	0.96	0.01	0.98	0.85	1.13	0.77
3+	0.67	0.51	0.88	0.004	0.76	0.55	1.04	0.08
CCM missing	0.82	0.75	0.88	<0.001	0.91	0.83	1.00	0.06
No HES link	0.46	0.39	0.54	<0.001	0.90	0.76	1.07	0.25
Timely GP referral				**<0.001**				**<0.001**
No GP referral	1.00				1.00			
FHA<=14 days	1.42	1.32	1.52	<0.001	1.24	1.14	1.34	<0.001
FHA>14 days	2.08	1.90	2.28	<0.001	1.80	1.62	1.99	<0.001
Type of treatment								**<0.001**
No treatment					1.00			
Surgery					44.34	39.20	50.15	<0.001
Surgery + chemo/radiotherapy					19.90	16.68	23.74	<0.001
Chemotherapy					2.13	1.82	2.50	<0.001
Chemotherapy +radiotherapy					5.81	5.06	6.68	<0.001
Radiotherapy					2.73	2.45	3.05	<0.001

[1] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, timely GP referral

[2] Mutually adjusted for SEP, age, sex, histology, year of diagnosis, co-morbidity score, timely GP referral, type of treatment

Chapter 15. References

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