Radiotherapy Dose-Fractionations and Outcomes in Cancer Patients

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Bias cannot usually be totally eliminated from epidemiological studies. The aim, therefore, must be to keep it to a minimum, to identify those biases that cannot be avoided, to assess their potential impact, and to take this into account when interpreting results. The motto of the epidemiologist could well be "dirty hands but a clean mind" (manus sordidae, mens pura).

- Geoffrey Rose, *Epidemiology for the uninitiated*

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Abstract

Radiotherapy cures many cancers, but the optimum total doses and fractionations used to treat different cancer types remain uncertain. While conventional fractionation (≈2 Gy per fraction) is common in many countries, UK practice has been highly variable.

This thesis compared different curative-intent radiotherapy dose-fractionations used in non-small cell lung and breast cancer. These two cancers together make up over a quarter of UK cancer incidence and mortality, and radiotherapy can increase cure rates of both cancers.

Two studies were conducted: (A) A meta-analysis of randomised radiotherapy trials in non-small cell lung cancer and (B) A cohort study of non-small cell lung and breast cancer radiotherapy in the Thames Valley.

For the meta-analysis, a systematic search was conducted. Eligible studies were randomised comparisons of two or more radiotherapy regimens. Median survival ratios were calculated for each comparison and pooled. 3,795 patients in 25 randomised comparisons of radiotherapy dose were studied. When radiotherapy was given alone, the higher dose within-trial resulted in increased survival (median survival ratio 1.13, 95% confidence interval 1.04-1.22). When radiotherapy was given with concurrent chemotherapy, the higher dose within-trial resulted in decreased survival (median survival ratio 0.83, 95% confidence interval 0.71-0.97).

For the cohort study, multiple Public Health England data sources were combined to obtain information on radiotherapy, patient characteristics, and outcomes. Multivariable Cox regressions were conducted separately by cancer site. 324 non-small cell lung, 8,879 invasive breast, and 477 ductal carcinoma in situ patients were studied. In analyses of both non-small cell lung and invasive breast cancer, increasing radiotherapy dose was associated with improved survival in some treatment centres, while in other centres the opposite was true. These opposite trends by treatment centre were unlikely to be explained by chance, and they suggest that differences in patient selection were driving results. There were insufficient events among ductal carcinoma in situ patients to assess associations.

Findings from the meta-analysis support consideration of further radiotherapy dose escalation trials, making use of modern methods to reduce toxicity. Findings from the cohort study suggest that it is not possible to use observational studies to examine causal effects of radiotherapy dose-fractionation. This thesis therefore shows the continued importance of conducting sufficiently large randomised trials to ascertain optimal dose-fractionation in radiotherapy.

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Contents

This thesis contains approximately 43,000 words.

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Abbreviations

ASTRO – American Society for Therapeutic RadiOlogy

BC – Breast Cancer

BCS – Breast Conserving Surgery

BED – Biologically Effective Dose

CAS – Cancer Analysis System

CHART – Continuous, Hyperfractionated, Accelerated RadioTherapy

CHHiP -- Clinical Study of Hypofractionation in Prostate Cancer

CI – Confidence Interval

CIA – Clinical Information Analysis dataset

COSD – Cancer Outcomes Services Dataset

CRUK – Cancer Research UK

CT – Chemotherapy

CTSU – Clinical Trial Service Unit (unit within which this DPhil was conducted)

CWT – Cancer Waiting Times dataset

DCIS – Ductal Carcinoma In Situ

DID – Diagnostic Imagining Dataset

DNA – DeoxyriboNucleic Acid

DOI – Digital Object Identifier

DPhil – Doctor of Philosophy

EBCTCG – Early Breast Cancer Trialists Collaborative Group

ENCORE – English Online Registration Environment

EQD2 – EQuivalent Dose in 2-Gray fractions

EQD2T – EQuivalent Dose in 2-Gray fractions, corrected for treatment Time

FAST (FAST-Forward) – FASTer radiotherapy for breast cancer patients (two trials)

FRCR – Fellow of Royal College of Radiology

FInstP – Fellow of Institute of Physics

GLOBOCAN – GLObal Burden Of CANcer study

GP – General Practitioner

HER-2 – Human Epidermal growth factor Receptor 2

HES – Hospital Episodes Statistics

HR – Hazard Ratio

HRG – Healthcare Resource Group

ID – IDentifier

IMD – Indicators of Multiple Deprivation score

IMRT – Intensity Modulated RadioTherapy

IRAS – Integrated Research Application System

KIT – Knowledge and Intelligence Team (cancer registration service)

LC – Lung Cancer

LR – Likelihood Ratio

LSOA – Lower Super Output Area (census area level used by Indices of Multiple Deprivation)

MDT – Multi-Disciplinary Team

MRC – Medical Research Council

NCDR – National Cancer Data Repository (old system prior to CAS)

NCIN – National Cancer Intelligence Network

NHS – National Health Service

No. – number

NRES – National Research Ethics Service

NSCLC – Non-Small Cell Lung Cancer

OCIU – Oxford Cancer Intelligence Unit

ONS – Office of National Statistics

PHE – Public Health England

PRISMA – Preferred Reporting Items for Systematic reviews and Meta-Analyses

PSA – Prostate Specific Antigen

RCR – Royal College of Radiologists

RT – RadioTherapy

RTDS – RadioTherapy DataSet

RTOG – RadioTherapy Oncology Group

SACT – Systemic Anti-Cancer Treatment dataset

SCC – Squamous Cell Carcinoma

SCLC – Small Cell Lung Cancer

SE – Standard Error

START – UK STAndardisation of breast RadioTherapy

TCR – Trent Cancer Registry

TNM – Tumour, Node, Metastasis (combination of information use for staging cancers)

UK – United Kingdom

Chapter 1

Background

1 Introduction

Radiotherapy is an important treatment for many types of cancer and has been in use for 120 years. It is estimated that more than half of all cancer patients receive radiotherapy at some point during their treatment (1). Delaney *et al* produced a table which depicts cancer types by the proportions of patients who should receive radiotherapy if treated according to guidelines (Table 1.1) (2). The table was based on the Australian population and Australian radiotherapy guidelines in 2003. Overall, 52% (95% CI 51%-53%) of patients were meant to receive radiotherapy in the treatment of their cancer, ranging widely, from 0% of liver cancer patients to 92% of cancers of the central nervous system, with a median across the different cancers of 57%.

Radiotherapy can be used to treat patients either curatively or palliatively. The aim of treating cancer patients with curative intent is to eliminate all cancer cells while adequately sparing normal surrounding tissues. Palliation aims to reduce symptoms and sometimes to prolong life, but it does not aim to remove the cancer entirely.

Over the past century, many different types of radiotherapy regimens have been used. It has become evident that how overall dose is divided into smaller doses is important in the effects of radiotherapy, both on tumours and on normal tissues. The aim of this DPhil was to study radiotherapy of curative intent and specifically to assess whether differences in how radiotherapy dose is divided into smaller doses result in different long-term outcomes in cancer patients.

Table 1.1 Optimal radiotherapy utilisation rate by cancer type

Tumour type	Proportion of all cancers (%)	For each cancer, proportion of patients receiving radiotherapy (%)	Across all cancers, proportion of patients receiving radiotherapy (%)
Breast	13	83	10.8
Lung	10	76	7.6
Melanoma	11	23	2.5
Prostate	12	60	7.2
Gynaecological	5	35	1.8
Colon	9	14	1.3
Rectum	5	61	3.1
Head and Neck	4	78	3.1
Gall bladder	1	13	0.1
Liver	1	0	0.0
Oesophageal	1	80	0.8
Stomach	2	68	1.4
Pancreas	2	57	1.1
Lymphoma	4	65	2.6
Leukaemia	3	4	0.1
Myeloma	1	38	0.4
Central nervous system	2	92	1.8
Renal	3	27	0.8
Bladder	3	58	1.7
Testis	1	49	0.5
Thyroid	1	10	0.1
Unknown primary	4	61	2.4
Other	2	50	1.0
Total	100	-	52.3

Source: Delaney et al (2)

2 Radiotherapy dose-fractionation

Radiotherapy kills cells, but cancer cells are usually more sensitive to radiation than surrounding normal tissues. This is why radiotherapy is used in the treatment of many cancers. The dose in curative intent radiotherapy in the UK varies from 20 Gy in early-stage Hodgkin's lymphoma, seminoma and some skin cancers to up to 78 Gy in prostate cancer (3). Giving radiotherapy doses in this range in one big dose would cause the patient to suffer unacceptable damage to normal tissues and could kill the patient, as well as being less effective in killing cancer cells. However, if the total dose is divided into multiple smaller doses, the time between the doses allows normal tissues to recover. Cancer cells usually recover less quickly, so fractionating radiotherapy often kills cancer cells effectively while sparing normal tissues. In addition, more cancer cells can be targeted in multiple doses (see *reoxygenation* and *redistribution*, page 9). The process of dividing the total dose into smaller ones is called *dose-fractionation*, and each smaller dose is called a *fraction*. Radiotherapy dose is measured in Gray units, shortened to "Gy". One Gray represents the absorption of one joule of ionising radiation per kilogram of matter (4).

Time is also an important factor in radiotherapy. The total amount of time over which radiotherapy is given is important as tumour cells could start to repopulate rapidly if the radiotherapy is not delivered quickly enough (see page 8). The time between fractions is also important, as normal cells must have enough time to recover between fractions but tumour cells must not (see page 7).

In summary, it is known that curative-intent radiotherapy can reduce the chances of cancer recurrence and death. It is also known that fractionating radiotherapy dose is beneficial. However, it is not known which total dose, dose per fraction, and treatment time are optimal for many cancers.

2.1 History of radiotherapy dose-fractionation

As described in the introduction to the seminal 2006 *Radiotherapy Dose-Fractionation* report by the Royal College of Radiologists (RCR), the process of developing radiotherapy in use today has been an "empirical art" rather than solely based on evidence (3). The first modern randomised clinical trial, the gold standard for scientifically assessing medical evidence, was published by Bradford Hill in 1948, investigating streptomycin to treat tuberculosis (5, 6). By the time of this randomised trial, radiotherapy had already been in use for over fifty years, and the development of radiotherapy in the treatment of patients up to that point had not been based on randomised evidence.

The first time radiotherapy was used to treat a patient was by Freund in Vienna, in 1896 (7). In the following decades, practitioners across Europe experimented with a variety of radiotherapy techniques. Ailments treated in this early period varied and included systemic lupus erythematodes, psoriasis, sarcoma, mycosis fungoides, leukaemia, breast cancer, and skin carcinoma (8). As early machines were limited technically, dose was given in a number of sessions, rather than in one big dose. Once machines were improved, it was found that bigger doses per session were no more effective than a higher number of smaller doses.

But debates existed about whether more smaller doses or fewer bigger doses should be given (3). In the early 1930s, the concept of giving multiple doses in a day with rest periods in between was developed (now called *acceleration*). Schwarz gave three times daily regimens of either 0.7 Gy, with intervals of 4 hours, or of 1 Gy, with intervals of 8 hours (8, 9). By contrast, in Manchester also in the 1930s, Patterson developed a regimen in which patients received less than one fraction per day (*hypofractionation*) due to machine capacity constraints: 45 Gy in 16 fractions, given over three weeks (10). In France, longer low-dose regimens were favoured (*hyperfractionation*). Coutard treated laryngeal patients in the 1920s with one or two daily fractions over 4-6 weeks (8, 11), and Baclesse treated breast cancer patients with 1.8 Gy daily up to four months (12). Trained

in Paris, Fletcher took with him to the United States his belief in longer radiotherapy regimens, and in the United States there is still a belief that treatment with fewer than 30 fractions is dangerous (12). From this practice, a convention of 2 Gy or slightly less per fraction given once per day was developed there (13). Over time, this convention was widely adopted internationally.

3 Radiobiological theory

Following clinical experiments in the early decades, theories about the underlying biology of radiotherapy began in the 1930s when Strandqvist examined treatment time-and-dose relationships, studying the effects of radiotherapy on skin (14). Building on this work, Ellis in the 1960s developed Nominal Standard Dose, a mathematical model allowing the first attempts to convert from one fractionation to another (15). In the early 1980s, a linear quadratic formula representing the surviving fraction of cells was proposed. In 1989, this was followed by the related concept of biologically effective dose (16, 17). Today, the linear quadratic formula and formulae for biologically effective dose remain optimal models in radiation biology (page 11). Throughout time, such mathematical models have been influenced by outcomes seen in medical practice, and in turn they have also influenced medical practice.

3.1 The Six "R"s of radiotherapy

Today, while it is not known which are optimal radiotherapy doses and fractionations, there are multiple theoretical elements known to play a role in radiobiology, which underpin radiotherapy dose-fractionation. These can be summarised as the "six Rs" of radiobiology, which are fundamental to understanding the multiple inter-related reasons why radiotherapy is fractionated. Originally, four "R"s were proposed: repair, repopulation, reoxygenation, and redistribution along the cell cycle. To these was added a fifth: radiosensitivity. And recently a sixth "R", remote bystander effects, has also been proposed (18).

3.1.1 Repair

Repair refers to cells recovering after being irradiated and is the most important element in dose-fractionation. Radiotherapy damages cells, some of which die and some of which recover. It is not desirable for cancer cells to repair themselves, but it is desirable for normal cells to repair themselves. Dose-fractionation is a useful strategy in delivering radiotherapy because tumour

cells are generally less good at repairing themselves than normal cells. Figure 1.1 is a simple model of the number of surviving healthy and tumour cells over time, with fractionation (left panel) and without (right panel) (19). The figure shows that over time fractionation permits normal tissues to recover, while tumour cells recover less (left panel). Without fractionation, normal tissues would suffer unacceptable levels of damage at doses high enough to effectively target tumour cells (right panel).

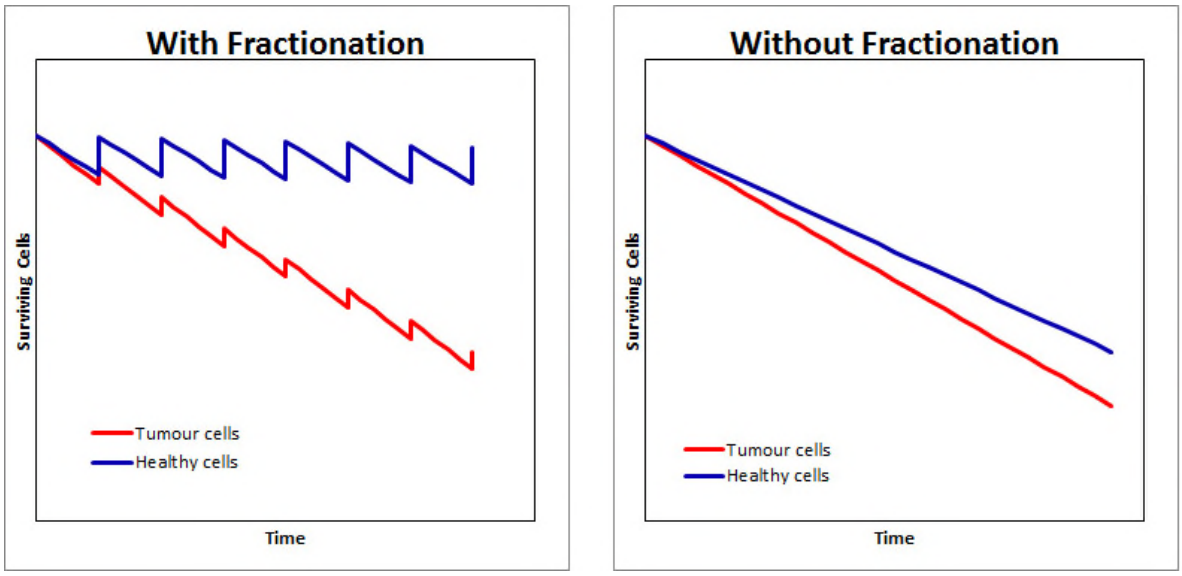


Figure 1.1: Recovery of tumour cells versus healthy cells, with fractionation and without. Reprinted from "The Five R's of Radiotherapy", available at http://www.radicalradiationremedy.com/the-five-rs-of-radiotherapy/, with permission from Radical Radiation Remedy Blog (19).

3.1.2 Repopulation

Repopulation refers to a tissue's response to cells being killed. If many cells in a tissue are killed, new cells are produced at a faster rate, to counteract the loss of dead cells. As with repair, repopulation of normal tissues is desirable, but not that of tumour cells. Repopulation of tumour cells is of great concern in radiotherapy (18). Repopulation of tumour cells can take some time, estimated to begin at about 21 to 28 days after the start of radiotherapy (20). Therefore, if the overall treatment time is more than 21-28 days, the efficacy of radiotherapy may be reduced as tumour cells may begin to repopulate, and they will reproduce at a faster rate. This is why overall treatment time is an important consideration, and why in this thesis an established biologically effect dose formula is used that includes a time factor (see page 11).

3.1.3 Reoxygenation

Reoxygenation refers to increasing access to oxygen for cells that remain alive after the first fractions of radiotherapy. Radiotherapy kills cells that are well-oxygenated most effectively. Tumour cells are often hypoxic, meaning that the intrinsic level of oxygen supply to these cells is low. This is because they have reduced access to blood vessels, especially in the centre of the tumour. However, as tumour cells are increasingly killed off by each radiotherapy fraction, the remaining hypoxic cells have better access to blood vessels, increasing their oxygenation and making them more susceptible to die from future radiotherapy fractions. Reoxygenation is one reason that fractionating radiotherapy dose is not only more effective in sparing normal tissues, but it also increases tumour cell kill.

3.1.4 Redistribution

Redistribution refers to the fact that, over time, individual cells move through different phases of the cell cycle. This matters because the sensitivity of cells to radiotherapy depends on which phase they are in. The cell cycle consists of four phases (Figure 2.2) (21). The length of each of the different-coloured arrows represents the proportion of time over one cycle that a cell spends in a given phase. Cells are longest in the G1 (gap) and S (DNA synthesis) phases. Cells are however most radiosensitive during the M phase (mitosis, or cell division) and late in the G2 (gap) phase, during which the cell prepares to enter the M phase (18). During any one fraction, cells that are currently in the M and late G2 phases are most efficiently

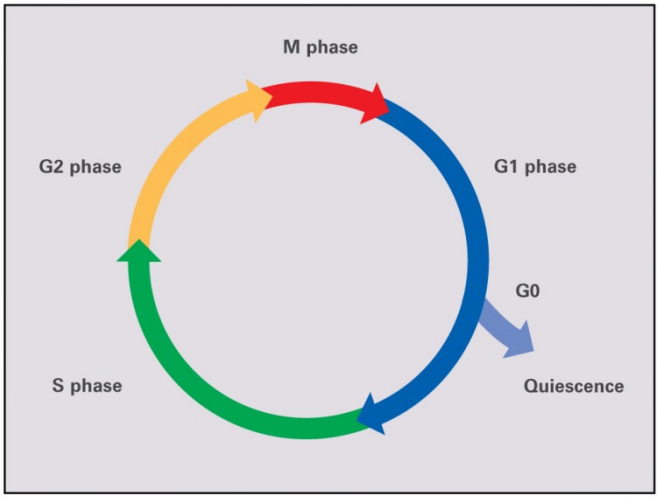


Figure 2.2: The four phases of the cell cycle.
Reprinted from National Institute of General Medical Sciences (21), with permission from image producers Crabtree & Company.

killed, while other cells survive. However, cell cycle redistribution over time ensures that at the next fraction, other cells will be in these sensitive phases and more cells will be killed.

3.1.5 Radiosensitivity

Radiosensitivity refers to the differences in response to radiotherapy between cells. Bergonie and Tribondeau first proposed in 1906 that cells that divide most rapidly are the most sensitive to radiation (22). Cellular radiosensitivity is therefore related to how quickly cells reproduce and how their reproductive capacity is affected by radiation (23). Undifferentiated and well-nourished cells tend also to be more radiosensitive (18).

Radiosensitivity is relevant to dose-fractionation because how the dose is best fractionated differs depending on radiosensitivity (23), which is related to the α/β ratio (see pages 11-12). Radiosensitivity is also relevant to determining which tumours may or may not be effectively treated with radiotherapy. Tumours that are intrinsically very radioresistent, such as malignant melanomas, are not effectively treated with radiotherapy.

3.1.6 Remote bystander effects

Remote bystander effects refer to a series of phenomena in which cells that are successfully killed by radiotherapy cause other, nearby cells to die also. This concept does not influence the way in which radiotherapy dose is fractionated. However, it is important for the consideration of other treatments that may increase the effectiveness of radiotherapy, such as gene therapy that could increase contact with nearby tumour cells, resulting in greater tumour cell kill (18).

3.1.7 Interplay of the six “R”s

These six “R”s of radiobiology are inter-related in their effects on dose-fractionation. Some of them would favour more fractions (repair of normal cells, re-oxygenation, redistribution), while others favour fewer fractions (repair of tumour cells, radiosensitivity in the case of tumours with

low alpha-beta ratios). While more treatment time between fractions would allow for greater repair of normal tissues, repopulation of tumour cells limits the overall treatment time that may be effective. Finding the right balance such that normal tissues are optimally spared but tumours are sufficiently irradiated is challenging.

3.2 The α/β ratio

The *α/β ratio* is an estimate of how easily cells in a given tissue type are irreparably killed by radiotherapy versus how quickly reparable cells recover after being irradiated (3). It has a number of applications, and is related both to cell repair and radiosensitivity. α and β are components of the linear quadratic equation, which describes cell kill over time after a single radiation dose:

$$Surviving\ fraction\ of\ cells = e^{-\alpha D-\beta D^2},$$

where *D* is the dose, *α* represents the linear initial slope of kill cell with a single radiation dose, and β represents the quadratic component of cell kill over time (24).

The ratio of α/β is an integral part of calculating biologically effective dose (BED), for which the formula used in this thesis is as follows:

$$\mathrm{BED} = Nd\left[1+\frac{d}{\alpha/\beta}\right] - k(T - T_{delay}),$$

where *N*=number of fractions, *d*=dose per fraction, *k*=biological dose needed to compensate for repopulation (see page 8) which is assumed to be 0.6 Gy (20, 25), *T*=total treatment time in days, and T_{delay}=time until onset of repopulation, assumed to be 21 days (20, 25). This is the most commonly used formula for BED that incorporates a time factor.

Whether an α/β ratio is high or low (whether repair is fast or slow, and whether cell reproduction is fast or slow) is important, as patients with tumours that have a higher alpha-beta ratio would benefit from fractionations that allow less tumour cell recovery between fractions (26). With some exceptions, normal tissues tend to have low α/β ratios, ranging from about 1-5 Gy (1).

Cancer cells generally have higher α/β ratios, but their range is wider, from about 0.5-2 Gy in prostate cancer (27) to about 14 Gy in laryngeal cancer (28).

The α/β ratio for many cancers is unknown, and there is variation between individual patients. A common estimated α/β ratio for cancers is 10 Gy if no better estimate is available (26). However, in breast and prostate cancers, the α/β ratio is thought to be much lower. The α/β ratio for breast cancer has been estimated to be 4 Gy using human data from randomised trials (29-31). In prostate cancer, the α/β ratio has also been studied using human data and could be even lower than in breast cancer (possibly in the range of 0.5-2 Gy) (27). In lung cancer, α/β ratios are less-well known and generally assumed to be 10 Gy (25, 26).

3.3 Altering conventional dose-fractionation

Based on the international convention of 2 Gy once-per-day fractions, various alterations have been suggested to accommodate differences in response to radiotherapy by various tumours and surrounding normal tissues. The most common such alterations to conventional fractionation are *hypofractionation*, *hyperfractionation*, and *acceleration*.

In *hypofractionation*, the dose per fraction is more than 2 Gy. For example, the Clinical Study of Hypofractionation in Prostate Cancer (CHHiP) trial randomised patients either to conventional fractionation or one of two hypofractionated arms (32). In the conventional arm, patients were given 74 Gy over 7.4 weeks in 37 once-per-day fractions of 2 Gy each. In the hypofractionated arms, patients were either given 60 Gy over 4 weeks in 20 once-per-day fractions of 3 Gy each, or they were given 57 Gy over 3.8 weeks in 19 once-per-day fractions of 3 Gy each. Sometimes in hypofractionation fractions are given less often than every day. For example, a fractionation commonly used at Oxford University Hospitals in the early to mid-2000s for breast cancer patients was 41.6 Gy over five weeks, given in 13 fractions of 3.2 Gy each, alternating 3 fractions or 2 fractions per week.

In *hyperfractionation*, the dose per fraction is decreased to below the conventional 1.8-2 Gy. For example, a randomised trial in head and neck patients compared conventional treatment of 66-70 Gy in 33-35 once-per day fractions of 2 Gy each with hyperfractionated treatment of 60-64 Gy in 38-40 fractions, giving two fractions per day of 1.6 Gy each (33).

In *acceleration*, the same total dose is given over a shorter overall treatment time, often by giving multiple fractions per day or by delivering radiotherapy also on the weekends. Acceleration and hyperfractionation are often combined. In the above example given for hyperfractionation, this regimen was also accelerated, because two fractions of 1.6 Gy each were given per day. The overall treatment time was reduced from 6.5-7 weeks in the conventional regimen to 4 weeks in the hyperfractionated, accelerated regimen.

Another altered fractionation strategy used more commonly in the past was *split-course* radiotherapy, in which a break in the treatment was given, usually for several weeks half-way through the course. A trial of NSCLC that started in 1992 randomised patients in the experimental arm to a split-course regimen that was also hyperfractionated: patients received 60 Gy in 40 fractions of 1.5 Gy each given twice per day. After the first 30 Gy, patients received a break of two weeks, after which the final 30 Gy were given (34).

3.4 Dose constraints and side effects

In order to kill a tumour, it would be optimal to irradiate cells with the highest-possible dose. However, normal tissues have a limit as to how much dose they can tolerate. These limits range widely between normal tissue types; published constraints vary from 1.5 Gy (testes) to 100 Gy (uterus) (1).

The types of reactions to radiotherapy exhibited by normal tissues also range in timing, type and degree of severity (1). Some reactions are short-term, such as sore throat or redness of skin, which may occur during radiotherapy and are usually reversible. Other reactions are long-term,

such as tissue fibrosis or ischaemic heart disease. While some reactions happen during radiotherapy or soon after, others can take several months or even years to appear.

The likely severity of radiation side effects and dose constraints of organs within the radiation field are key determinants of the total radiation dose used to treat tumours. Dose-fractionation can help to spare normal tissues, but the total dose remains limited by these side effects.

4 Radiotherapy dose-fractionation practices in the UK over the past three decades

By the time the 2006 *Radiotherapy Dose-Fractionation* report was written, the international convention had formed around practices in the United States, where doses of around 2 Gy per fraction were the standard of treatment (13). However, within the UK variation in practice was still widespread (3). A survey in 1989 asked UK Clinical Oncologists about the fractionation schedule they would prescribe in six hypothetical patient scenarios (35). The authors found that most consultants used different fractionation schedules for each of the six scenarios, with schedules ranging from 6 to 45 fractions for a given curative situation and 1 to 36 fractions for a given palliative one.

A study in 2003 examined dose and fractionation in a one-week audit of all radiotherapy treatments in the UK. It found that, although radiotherapy schedules were more consistent than in 1989, they still varied. Figure 1.3 displays the variability in lung cancer treatment (36). A further study found that the four radiotherapy centres serving the Thames Valley area between 1999 and 2009 used a wide variety of fractionation regimens for adjuvant breast cancer radiotherapy (Figure 1.4) (37).

This diversity in UK practice was the motivation behind the publication of the first Radiotherapy Dose-Fractionation report in 2006 (3). In 2012, at the start of this DPhil, although breast radiotherapy had become more uniform in the UK, practices still remained highly variable for many cancers, including prostate, lung, and head and neck cancers (38). Such variability in UK data was an opportunity to research what effects different radiotherapy dose-fractionations might have in the long-term.

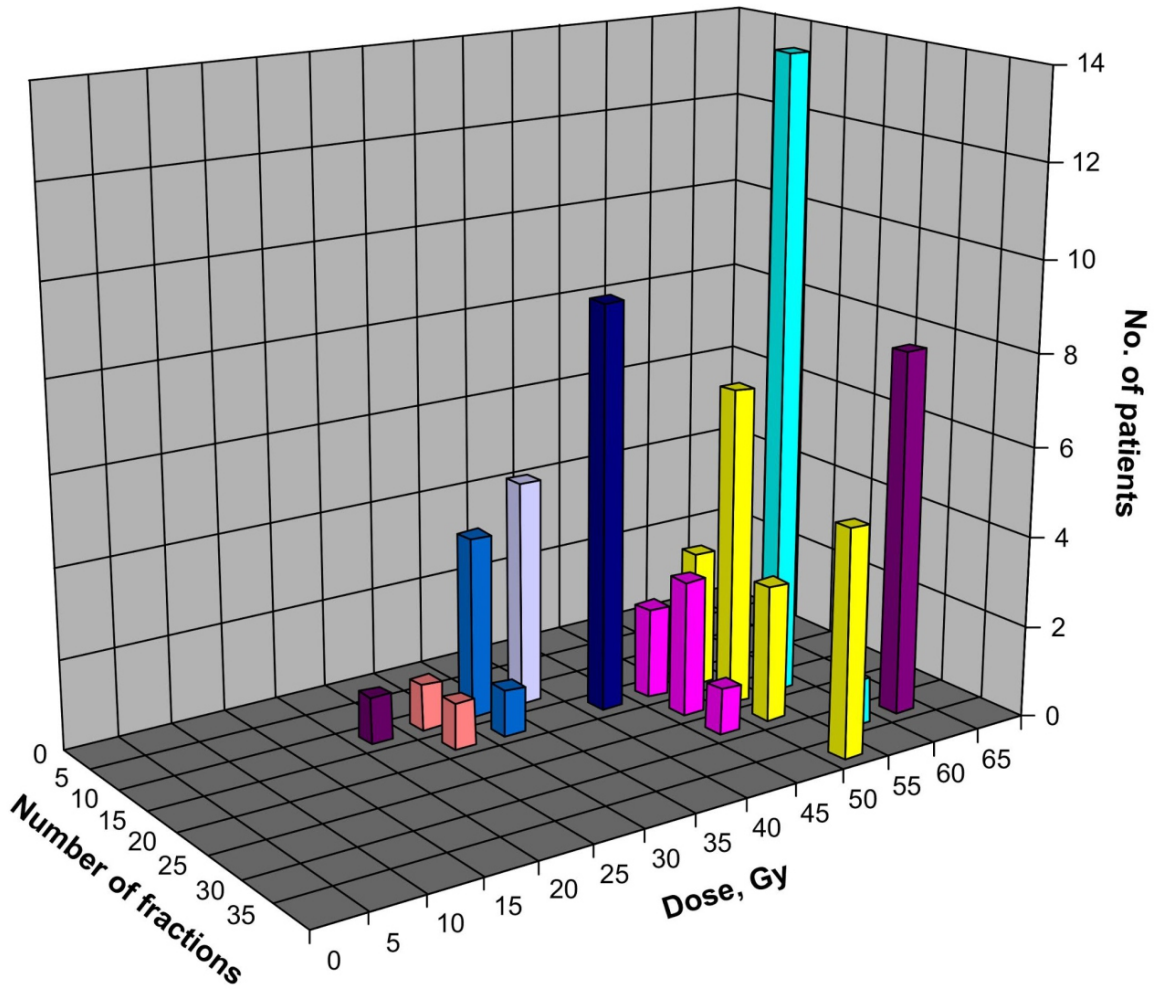
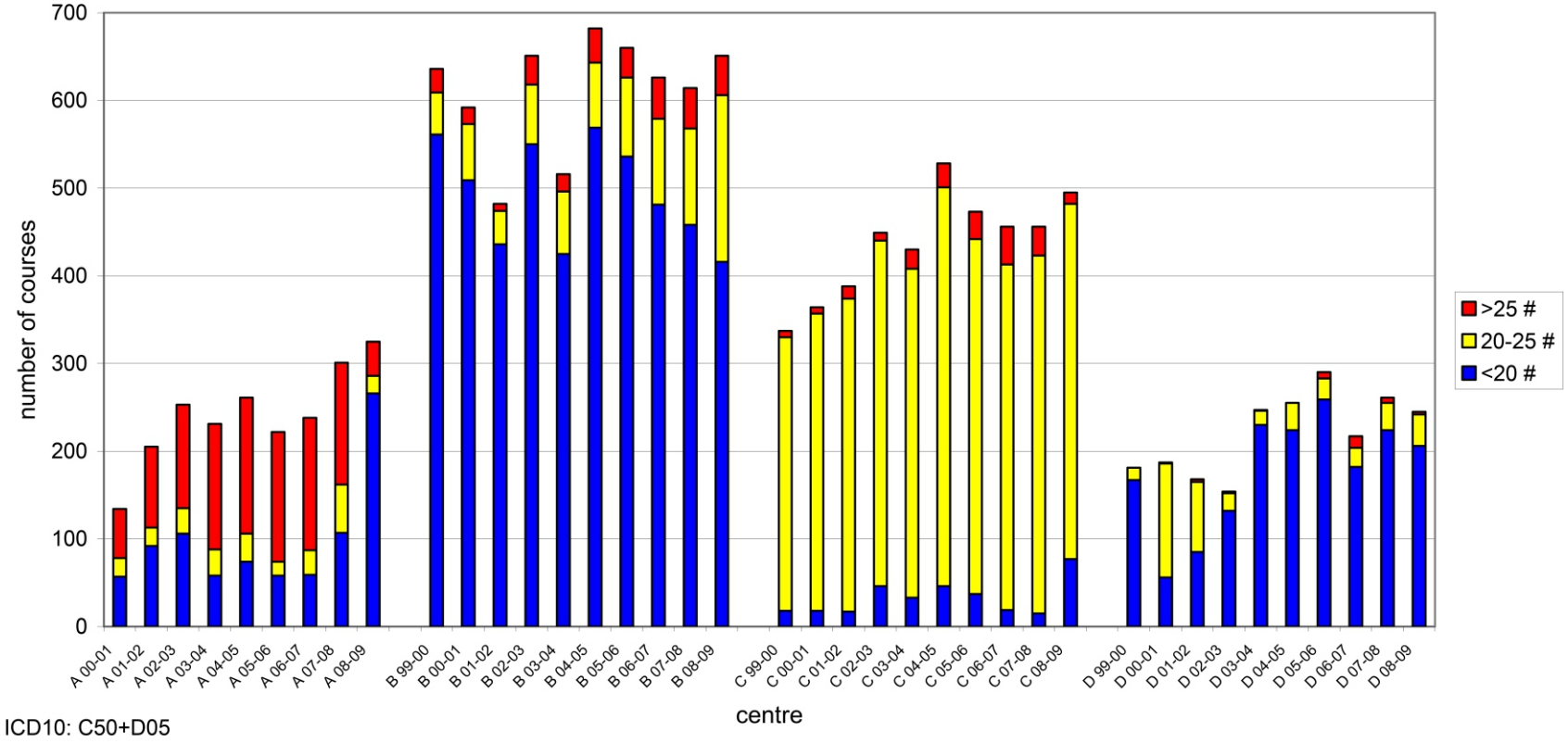


Figure 1.3: Numbers of patients treated using different fractionation schedules for radical lung cancer treatment in 2003 in the UK (37).



ICD10: C50+D05

Figure 1.4: Trends in breast cancer radical fractionation schedules by year for four centres in the Thames Valley. Centres denoted by A, B, C, D. Calendar years by 99-01 (ie 1999-2001), 00-01, ..., 08-09. Schedules are blue: <20 fractions, yellow: 20-25 fractions, red: >25 fractions (38).

5 Observational versus randomised evidence

Randomised trials are the gold standard for comparing experimental treatment regimens with conventional ones. If well-conducted, randomisation eliminates confounding by known and unknown factors. In a study aiming to measure the association between radiotherapy dose-fractionation and survival, radiotherapy dose-fractionation is the main independent factor of interest and survival is the outcome. If factors are confounders, they must be independently associated with both the main independent factor of interest and with the outcome. For example, age may be a confounder of dose-fractionation and survival. In a non-randomised clinical setting, older patients may systematically receive different dose-fractionations to younger patients. They are also more likely to die, and they may be more likely to die of cancer-specific causes. However, in a randomised trial, older and younger patients are randomly assigned to different dose-fractionations, so age will not confound the association measured between dose-fractionation and survival.

In observational studies, patients are not randomised but rather they receive the treatment regimen their clinician deems best. An association measured in an observational study between dose-fractionation and survival could therefore be potentially confounded by a number of factors (for example age, comorbidity, stage of disease, tumour size, or any other treatments received). Continuing the above example with age as a confounder, a crude association of dose-fractionation and survival in an observational study is likely to be biased by the underlying associations with age. Multi-variable analytical methods do, however, make it possible to take account of this underlying confounding by age. If information on all confounders can be reliably measured and is accounted for in multi-variable analyses, then an observational study has the potential to be of high quality and could provide valuable contributions to medical knowledge.

A potential advantage of observational studies over randomised trials is that patients in observational studies are often more representative of the overall patient population receiving the treatments being studied. In randomised trials, the aim is to quantify the pure medical effect of a treatment, and not to determine how effective it is in a population of patients with a range of other factors (for example, they may be taking multiple other treatments, or some patients may be otherwise very ill). To this end, patients are selected so that the effects of treatments measured are less likely to be diluted by other factors, so usually only the fittest patients are eligible for trials. In fit patients, treatments are more likely to be effective and well-tolerated, and any events that occur (such as deaths) are less likely to occur because of other underlying reasons that were present before treatment began. Therefore, results of a high-quality observational study have the potential to be more informative than randomised trials about the effectiveness of treatments for patients in the overall population.

Much of the evidence that informed recommendations in the 2006 RCR Dose-Fractionation Report came from cohort studies, rather than from randomised trials (3). The report concluded that further observational studies should continue to be conducted, as these can contribute to more rapid progress in the assessment of radiotherapy dose-fractionation. Care should be taken that such studies be well-designed. It was recommended that routinely collected electronic data be used to conduct prospective cohort studies. Such studies would have the advantage of making use of many patients, increasing statistical power. They would also have the advantage of being comparably cheaper than randomised trials. As routine data collected in the past could be used, results could be obtained more quickly than in randomised trials, which usually require years of patient follow-up to be informative.

6 Aims of the DPhil and structure of the thesis

6.1 Aims of the DPhil

The aim of this DPhil was to use an epidemiological approach to study relationships between radiotherapy fractionation and long-term outcomes in cancer patients. Given the variability in UK radiotherapy dose-fractionation practices, it was decided to search for an appropriate observational UK dataset that would enable a high-quality cohort study using electronic routinely collected data. Results of this cohort study could be compared with results of large randomised trials and meta-analyses of randomised trials.

It was decided to focus on two cancer sites: non-small cell lung cancer (NSCLC) and breast cancer. Both of these cancers contribute to a large proportion of cancer incidence and death in the UK (Chapter 4). In the UK in 2014, 15% of new cancer cases were invasive breast cancers and 13% were lung cancers; 7% of all cancer deaths were from invasive breast cancer and 22% from lung cancer (39). There are many breast cancer patients for whom radiotherapy is a component of curative treatment, and large randomised trials have been conducted with which the results of an observational study could be compared. There are not as many NSCLC patients treated with radiotherapy of curative intent as there are breast cancer patients (Chapter 4). However, NSCLC mortality is high, so there could still be a large number of events resulting in good statistical power. There are not many randomised trials of radiotherapy dose-fractionation in NSCLC with large numbers of patients, so it was decided that a meta-analysis of randomised trials in NSCLC would be necessary, in order to compare with observational results.

Therefore, two separate but related studies were conducted that compared multiple radiotherapy fractionation schedules for patients treated with curative intent for NSCLC and breast cancer:

A. A meta-analysis of randomised controlled trials in NSCLC patients;

B. A cohort study of NSCLC and breast cancer patients in the Thames Valley using Public Health England cancer registration data.

6.2 Structure of the thesis

This DPhil contains five chapters, including this introduction. Chapter 2 is a peer-reviewed publication of study A above, a meta-analysis of randomised controlled trials in NSCLC patients. It also contains additional material that was produced after publication.

Chapters 3 and 4 relate to study B above, a cohort study using Public Health England data from the Thames Valley. Chapter 3 describes how this cohort study was developed, challenges overcome, and lessons learned. Chapter 4 contains the main body of the study, with the standard structure of a scientific publication.

Chapter 5 is a summary of the DPhil, including the principal conclusions and implications of both studies, and suggesting future research on the subject of radiotherapy dose-fractionation.

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Chapter 2

Dose and fractionation in radiotherapy of curative intent for non-small-cell lung cancer: meta-analysis of randomised trials

1 Foreword

The text that follows in this chapter is adapted from a publication, accepted in the International Journal of Radiation Biology, Oncology, Physics on 15 July, 2016, and appearing online on 24 July, 2016. The authors on the publication were as follows: Johanna Ramroth[1] MSc, David J. Cutter[1] FRCR DPhil, Sarah C. Darby[1] PhD, Geoff S. Higgins[2] FRCR DPhil, Paul McGale[1] PhD, Mike Partridge[3] FInstP PhD, Carolyn W. Taylor[1] FRCR DPhil. Following this text is a section on additional material not included in the publication.

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2 Summary

We conducted a meta-analysis of overall survival in 3,795 patients with non-small-cell lung cancer who were randomised in 21 trials comparing higher versus lower radiotherapy doses of curative intent. In trials with chemotherapy, higher radiotherapy doses led to poorer survival but, in trials where chemotherapy was not given, higher time-corrected biologically effective doses resulted in longer survival. These findings support consideration of further trials of radiotherapy dose escalation within the context of toxicity reduction.

3 Abstract

Purpose The optimum dose and fractionation in radiotherapy of curative intent for non-small-cell lung cancer remains uncertain. We undertook a published data meta-analysis of randomised trials to examine whether radiotherapy regimens with higher time-corrected biologically effective doses resulted in longer survival, either when given alone or when given with chemotherapy.

Methods and materials Eligible studies were randomised comparisons of two or more radiotherapy regimens, with other treatments identical. Median survival ratios were calculated for each comparison and pooled.

Results 3,795 patients in 25 randomised comparisons of radiotherapy dose were studied. The median survival ratio, higher versus lower corrected dose, was 1.13 (95% CI 1.04-1.22) when radiotherapy was given alone, and 0.83 (95% CI 0.71-0.97) when it was given with concurrent chemotherapy (p for difference=0.001).

In comparisons of radiotherapy given alone, the survival benefit increased with increasing dose difference between randomised treatment arms (p for trend=0.004). The benefit increased with increasing dose in the lower-dose arm (p for trend=0.01) without reaching a level beyond which no further survival benefit was achieved. The survival benefit did not differ significantly between randomised comparisons where the higher-dose arm was hyperfractionated and those where it was not.

There was heterogeneity in the median survival ratio by geographical region (p<0.001), average age at randomisation (p<0.001) and year trial started (p for trend=0.004), but not for proportion of patients with squamous cell carcinoma (p=0.2).

Conclusions In trials with concurrent chemotherapy, higher radiotherapy doses resulted in poorer survival, possibly caused, at least in part, by high levels of toxicity. Where radiotherapy was given without chemotherapy, progressively higher radiotherapy doses resulted in progressively longer survival and no upper dose level was found above which there was no further

benefit. These findings support consideration of further radiotherapy dose escalation trials, making use of modern treatment methods to reduce toxicity.

4 Introduction

Lung cancer is the commonest cause of cancer death worldwide and survival has improved little since the mid-1970s, with ten-year survival at only 4% in 2011 (1, 2). Almost 90% of lung cancers are non-small-cell (NSCLC) (3) and surgery is the main curative treatment. Many patients are, however, inoperable at presentation (4) and, for them, radiotherapy of curative intent may be considered, possibly in conjunction with chemotherapy. Since the 1970s, conventional radiotherapy in NSCLC has been defined as 60-63 Gy in 1.8-2.0 Gy fractions (5-7) but several trials have considered alternatives. These include split-course radiotherapy (with a several-day break), hyperfractionation (multiple smaller daily doses), hypofractionation (fewer, larger-dose fractions), acceleration (delivering the same dose over a shorter period), or changing total dose while keeping the same dose per fraction. Changes to these parameters all affect the biologically effective dose (BED) and may alter tumour control probability.

No randomised trials of radiotherapy dose and fractionation in NSCLC have included more than 600 patients, and many have fewer than 200. Consequently, most have not, individually, had sufficient power to detect modest effects on survival which would be important clinically. Where significant effects have been seen in individual trials, they may reflect extremes in the play of chance. More powerful inferences can be obtained when the data from all trials addressing a particular question are combined in a meta-analysis. A number of meta-analyses of trials comparing different radiotherapy regimens in NSCLC have been conducted (8-10), but none has evaluated the effect of radiotherapy in terms of different levels of BED, and none has included all the relevant trials.

Several randomised trials have addressed the role of chemotherapy in addition to radiotherapy in NSCLC (11, 12). A Cochrane review of 3,752 patients in 25 trials concluded that concurrent chemoradiotherapy resulted in better survival than radiotherapy alone (hazard ratio,

chemotherapy versus not: (HR) 0.71, 95% CI 0.64 – 0.80) or radiotherapy with sequential chemotherapy (HR 0.74, 95% CI 0.62 – 0.89) (13). Therefore, over the past decade, this has become the 'standard of care' for locally advanced NSCLC patients. However, patients treated with chemoradiotherapy experience more toxicity than those treated with radiotherapy alone, particularly when chemotherapy is given concurrently (7, 13). Thus, within the context of chemoradiation, radiotherapy dose escalation may result in a level of toxicity that outweighs any benefit from improved tumour control.

Given ongoing uncertainty regarding the optimal dose for curative-intent NSCLC radiotherapy, and high levels of toxicity, it is not surprising that radiotherapy practice varies (12, 14, 15). Recent advances are, however, enabling radiotherapy to be delivered with lower toxicity than previously, and so knowledge regarding the optimal dose for curative-intent radiotherapy is becoming more important. We have, therefore, conducted a meta-analysis of published data from randomised trials comparing different radiotherapy regimens. Our aim is to examine whether radiotherapy regimens delivering higher corrected dose increase overall survival in NSCLC curative-intent radiotherapy, either when given alone or with chemotherapy.

5 Methods and Materials

5.1 Literature search and selection criteria

The Embase database was searched, using variations of the terms radiotherapy dose-fractionation, hyperfractionation, hypofractionation, accelerated radiotherapy, and lung cancer (Appendix 1, Supplementary Text 1). Studies starting between 1/1/1980 and 4/28/2015 were eligible if they included a randomised comparison of two or more external beam radiotherapy dose-fractionation regimens, with other treatments identical in any arms compared. A trial using hospital numbers to randomise was excluded (16).

5.2 Calculation of time-corrected equivalent dose in 2 Gy fractions (EQD2T)

To compare different dose-fractionation regimens, total doses were converted to time-corrected equivalent doses in 2 Gy fractions (EQD2T) as follows (17):

$$\mathrm{EQD2T} = \frac{\mathrm{BED}}{1+\frac{2}{\alpha/\beta}},$$

where α/β was assumed to be 10 and BED was defined as:

$$\mathrm{BED} = Nd\left[1+\frac{d}{\alpha/\beta}\right] - k(T - T_{delay}),$$

where N=number of fractions, d=dose per fraction, k=biological dose needed to compensate for repopulation which was assumed to be 0.6 Gy, T=total treatment time in days, and T_{delay}=time until onset of repopulation, assumed to be 21 days. For regimens lasting <21 days, k was set to zero (17).

5.3 Statistical analyses

Analyses were based on median survival times (18), extracted from trial publications for each arm. If not reported, they were derived from survivor function graphs or one-year survival. For each randomised comparison, a median survival ratio was calculated by dividing median survival in the

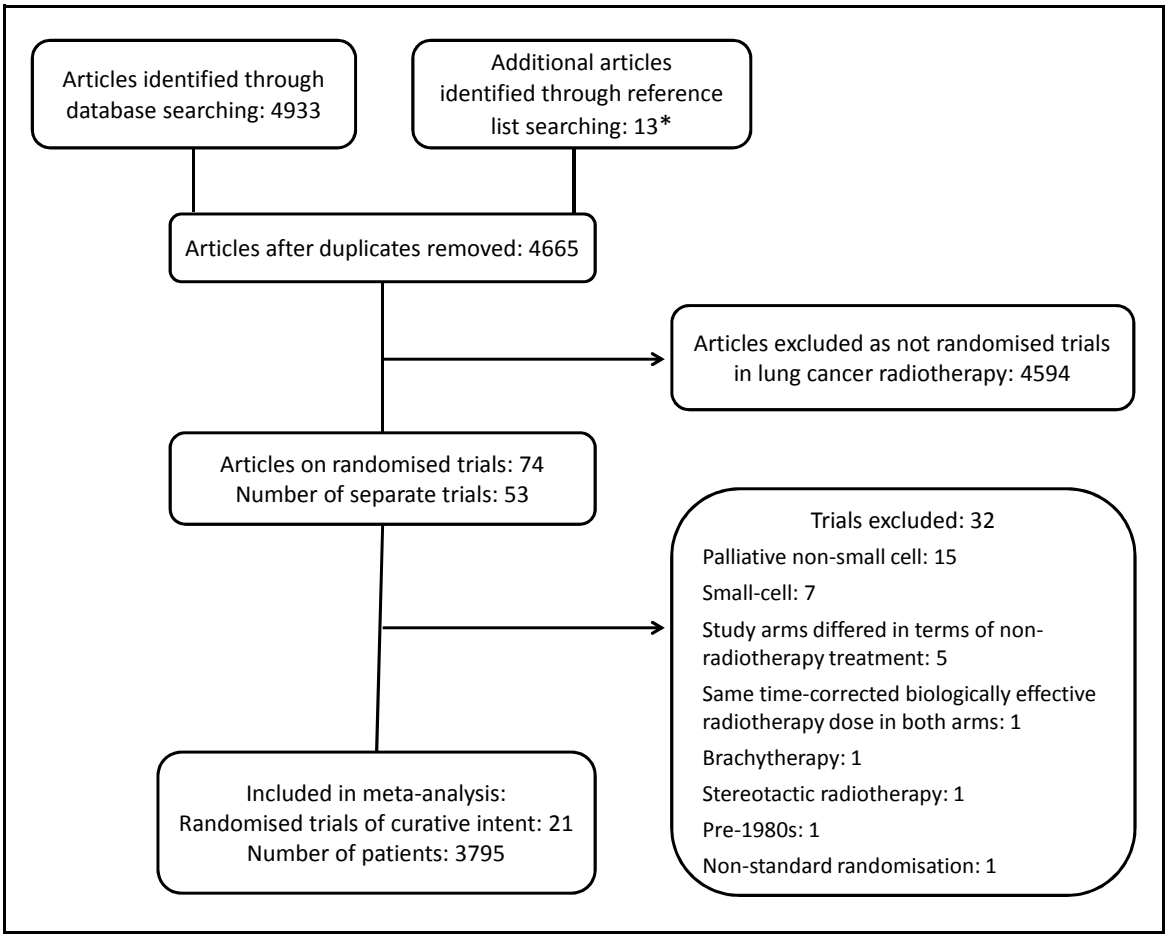
higher-dose arm by median survival in the lower-dose arm. For trials with more than two study arms, separate median survival ratios compared to the lowest-dose arm were calculated for every other trial arm, resulting in separate treatment comparisons. Confidence intervals and significance tests were based on standard errors (19). All analyses were conducted in Stata version 13.1 (20). Further methodological details are in Appendix 1, Supplementary Text 2.

6 Results

Twenty-one trials with 3,795 patients were included in the meta-analysis (Figure 2.1) (6, 21-40). Eight trials were conducted in China, seven in North America, four in Europe, one in South Asia, and one in Australia (Table 2.1). The number of patients per trial ranged from 30-563; years of randomisation from 1982-2011; and the average age at randomisation from 48-66 years (Appendix 1, Table 1). In the 18 trials reporting proportions of patients by cancer stage, 13 reported at least 94% of patients had stage III disease and five reported between 55% and 89% had stage III. Two trials had multiple arms, resulting in 25 randomised radiotherapy dose comparisons in 21 trials (Table 2.1). EQD2T doses within trial arms ranged from 36.4 Gy to 80.8 Gy (Appendix 1, Table 2), and EQD2T increased with calendar year (p=0.04, Appendix 1, Figure 1). The dose difference between trial arms ranged from 1.1 Gy to 27.2 Gy (Table 2.1) and in 12 of the randomised comparisons, dose escalation was achieved by hyperfractionation. Chemotherapy was given in 7 trials (2 sequential, 5 concurrent) and not given in 18. Median survival ranged from 6.3 to 29.9 months.

6.1 Effect of chemotherapy on dose escalation

The median overall survival ratio, higher versus lower EQD2T, pooled across all randomised dose comparisons was 1.07 (95% CI 1.00-1.15, p=0.05, Figure 2.2). When these comparisons were grouped according to whether the protocol specified no chemotherapy, sequential chemotherapy or concurrent chemotherapy the heterogeneity between these groups was highly significant (p=0.001). The median survival ratios were 1.13 (95% CI 1.04-1.22, p=0.002) without chemotherapy, 1.29 (95% CI 0.92-1.80, p=0.1) with sequential chemotherapy, and 0.83 (95% CI 0.71-0.97, p=0.02) with concurrent chemotherapy. Hence, radiotherapy dose escalation led to significantly better survival for comparisons without chemotherapy, but significantly poorer survival in comparisons with concurrent chemotherapy.



* Reference lists in publications for all trials included in the study as well as other meta-analyses of radiotherapy in lung cancer were searched to identify additional publications of trials missed in the search

Figure 2.1: Trial identification and selection.

Table 2.1. Descriptive summary of trials included in meta-analysis, by ascending EQD2T difference between trial arms

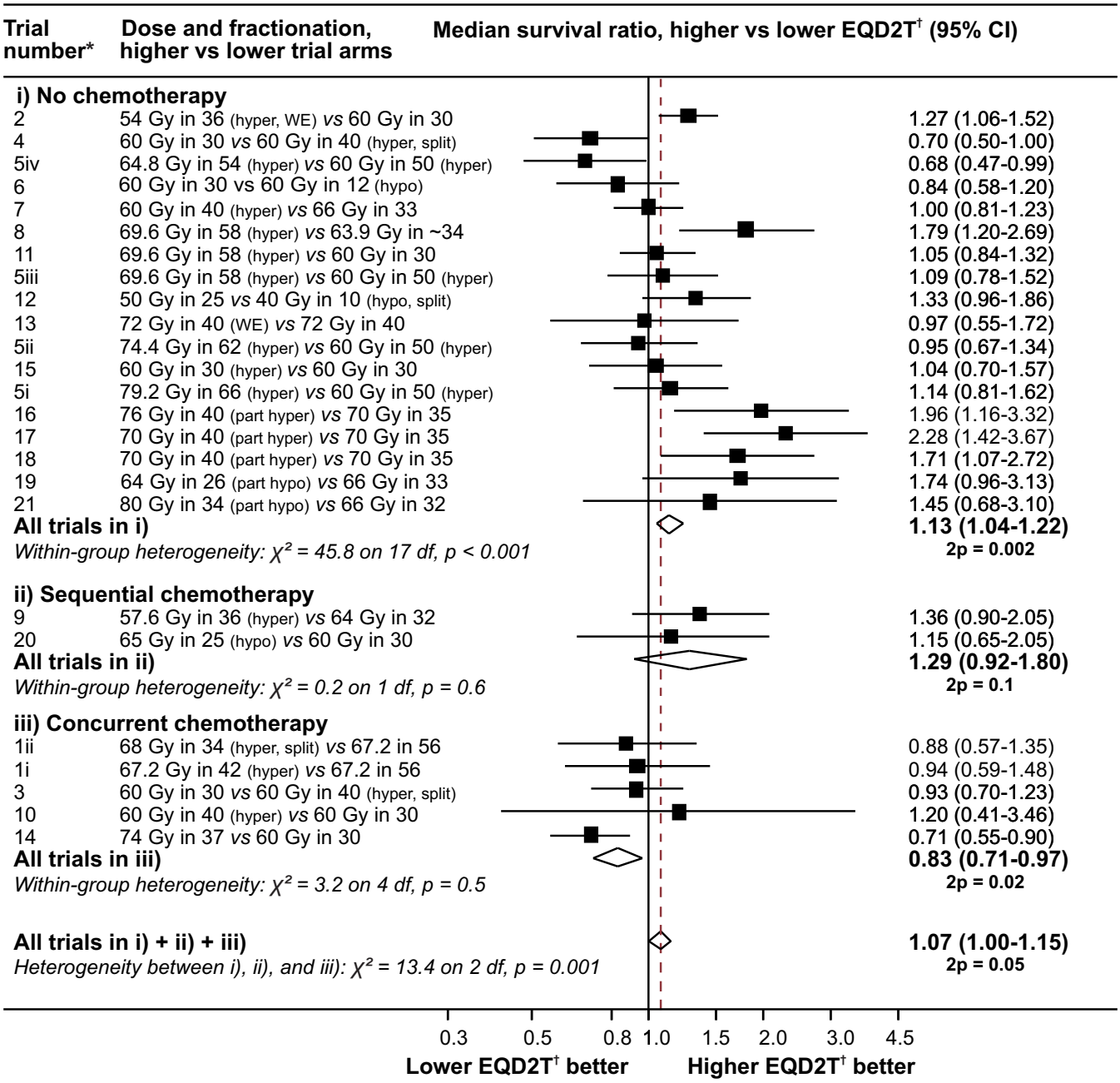
Trial no.	First author, year (reference)	Years of randomisation	Country	No. patients	EQD2T in each trial arm (Gy)	EQD2T difference between trial arms (Gy)	Chemo-therapy
1	Zhan, 2007 (35)	2000 - 2005	China	159	A: 56.2, B: 54.9, C: 53.8	1.1, 2.4 †	Concurrent
2	Saunders, 1999 (19)	1990 - 1995	UK, Germany, Sweden	563	A: 51.8, B: 49.7	2.1	None
3	Schild, 2002 (20)	1994 - 1999	US	234	A: 49.7, B: 47.2	2.5	Concurrent
4	Bonner, 1998 (21)	1992 -1993	US	67	A: 49.7, B: 47.2	2.5	None
5	Cox, 1990 (22)	1983- 1987	US	516	A: 61.5, B: 58.4, C: 55.4, D: 52.3, E: 49.2	3.1, 6.2, 9.2, 12.3 ‡	None
6	Slawson, 1988 (23)	1982 - 1986	US	120	A: 49.7, B: 46.5	3.2	None
7	Baumann, 2011 (17)	1997 - 2005	Germany, Poland, Czech Republic	406	A: 57.5, B: 53.6	3.9	None
8	Fu, 1994 (24)	1990 - 1992	China	105	A: 52.3, B: 48.3	4	None
9	Belani, 2005 (25)	1998 - 2001	US	119	A: 55.7, B: 51.6	4.1	Sequential
10	Sapkota, 2013 (26)	Not specified	India, Nepal	30	A: 54.2, B: 49.7	4.5	Concurrent
11	Sause, 2000 (27)	1989 - 1992	US, Canada	301	A: 55.4, B: 49.7	5.7	None
12	Reinfuss, 1999 (28)	1992 - 1996	Poland	160	A: 43.2, B: 36.4	6.8	None
13	Zajusz, 2006 (32)	2001 - 2006	Poland	53	A: 61.3, B: 53.5	7.8	None
14	Bradley, 2015 (6)	2007 - 2011	US, Canada	424	A: 58.8, B: 49.7	9.1	Concurrent
15	Ball, 1999 (18)	1989 - 1995	Australia	99	A: 60.0, B: 49.7	10.3	None
16	Zhu, 2000 (36)	1993 -1996	China	70	A: 68.8, B: 56.2	12.6	None
17	Cheng W, 2007 (34)	1999 - 2002	China	81	A: 68.8, B: 56.2	12.6	None
18	Cheng J, 2004 (33)	1995 - 1998	China	74	A: 68.8, B: 55.6	13.2	None
19	Wang, 2005 (29)	2001 - 2003	China	86	A: 68.8, B: 53.6	15.2	None
20	Yu, 2014 (31)	2009 - 2011	China	60	A: 68.8, B: 53.2	25.6	Sequential
21	Wang, 2008 (30)	2004 - 2006	China	68	A: 80.8, B: 53.6	27.2	None

For further details of study characteristics and treatments, see Tables E1 and E2.

* EQD2T is calculated in terms of 2 Gy biologically effective dose per fraction, corrected for total treatment time. Study arms are presented in order of ascending difference in EQD2T between trial arms; if there were multiple arms, study number was assigned based on the smallest dose difference.

† Three arm-study. Each of the higher-dose arms was separately compared to the lowest-dose arm as the baseline. Arm B vs C: 1.1 Gy difference. Arm A vs C: 2.4 Gy difference.

‡ Five-arm study. Each of the higher-dose arms was separately compared to the lowest-dose arm as the baseline. Arm D vs E: 3.1 Gy difference. Arm C vs E: 6.2 Gy difference. Arm B vs E: 9.2 Gy difference. Arm A vs E: 12.3 Gy difference.



Abbreviations: hyper = hyperfractionated (more than one fraction per day); WE = including weekends; split = split-course radiotherapy, minimum 10 day gap; hypo = hypofractionated (more than 2Gy per fraction); part hyper = partially hyperfractionated; part hypo = partially hypofractionated.

*studies are ordered within groups by ascending EQD2T difference between trial arms

† EQD2T is time-corrected equivalent dose in 2 Gy fractions

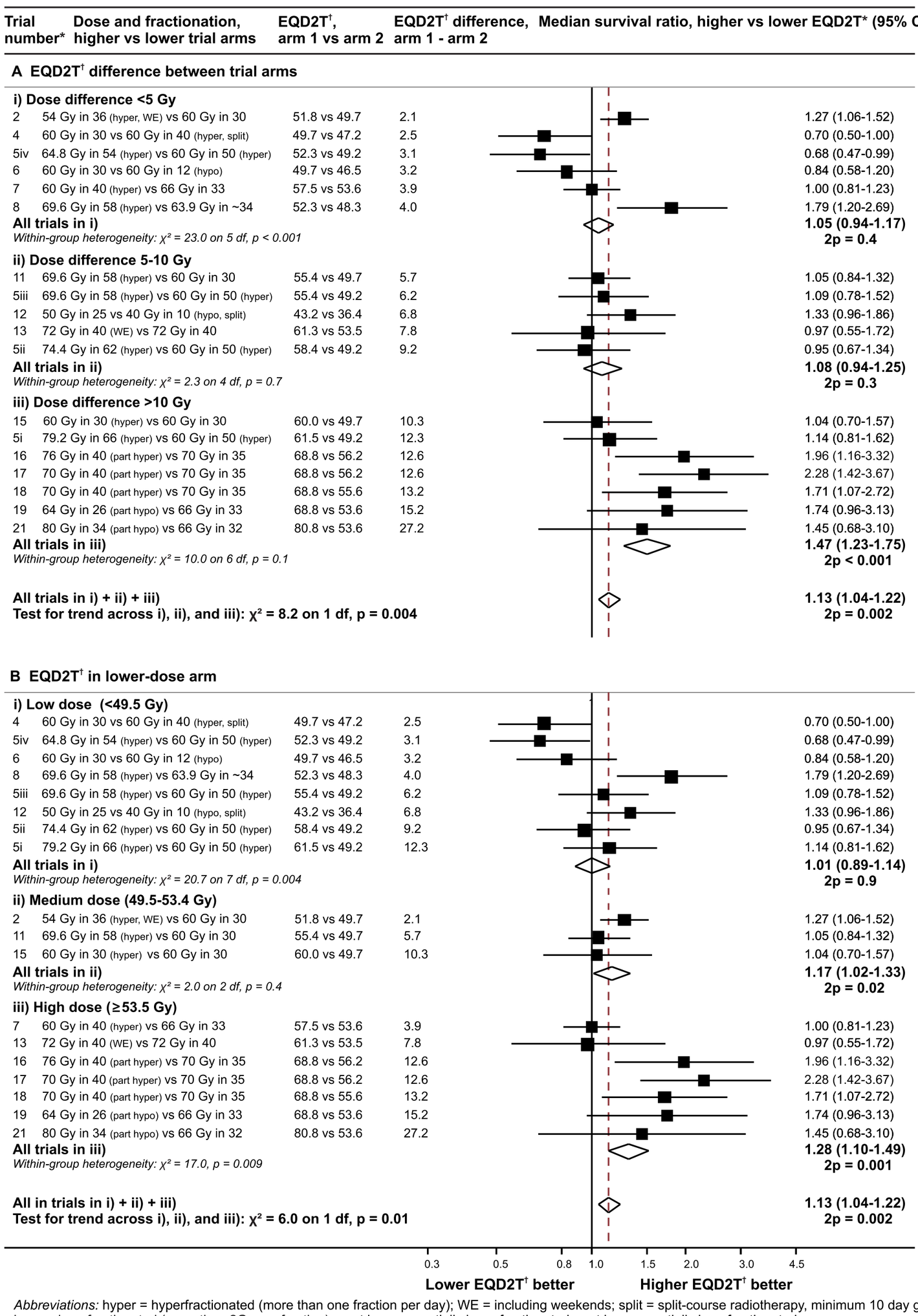
Figure 2.2: Median survival ratios, higher vs lower corrected radiotherapy dose (EQD2T), according to whether radiotherapy was given without chemotherapy, with sequential chemoradiotherapy, or with concurrent chemoradiotherapy.

For randomised comparisons that included concurrent chemotherapy, there was no significant heterogeneity between the median survival ratios (p=0.5), nor was there any trend with increasing EQD2T difference between arms (p=0.1). There were just two randomised comparisons with sequential chemotherapy, including 193 patients, so confidence intervals were wide.

6.2 Radiotherapy dose escalation without chemotherapy

For the 18 radiotherapy-only comparisons, the median survival ratio, higher versus lower radiotherapy dose, was 1.13 (95% CI 1.04-1.22) (Figure 2.2). When these comparisons were categorised according to dose difference between trial arms, the pooled median survival ratio for EQD2T differences of <5 Gy was 1.05 (95% CI 0.94-1.17, p=0.4), while for EQD2T differences of 5-10 Gy it was 1.08 (95% CI 0.94-1.25, p=0.3), and for EQD2T differences of >10 Gy, it was 1.47 (95% CI 1.23-1.75, p<0.001) (Figure 2.3, panel A). The increasing trend in median survival ratios across these three groups was highly statistically significant (p for trend=0.004), providing strong evidence that, without chemotherapy, survival increases with increasing EQD2T. When the dose comparisons with EQD2T difference ≥10 Gy between trial arms were further divided into trials in which hyperfractionation was used to escalate dose versus other trials, the median survival ratios did not differ significantly (1.60, 95% CI 1.27-2.02, and 1.29, 95% CI 0.98-1.71, p for difference=0.2) (Figure 2.4, panel A).

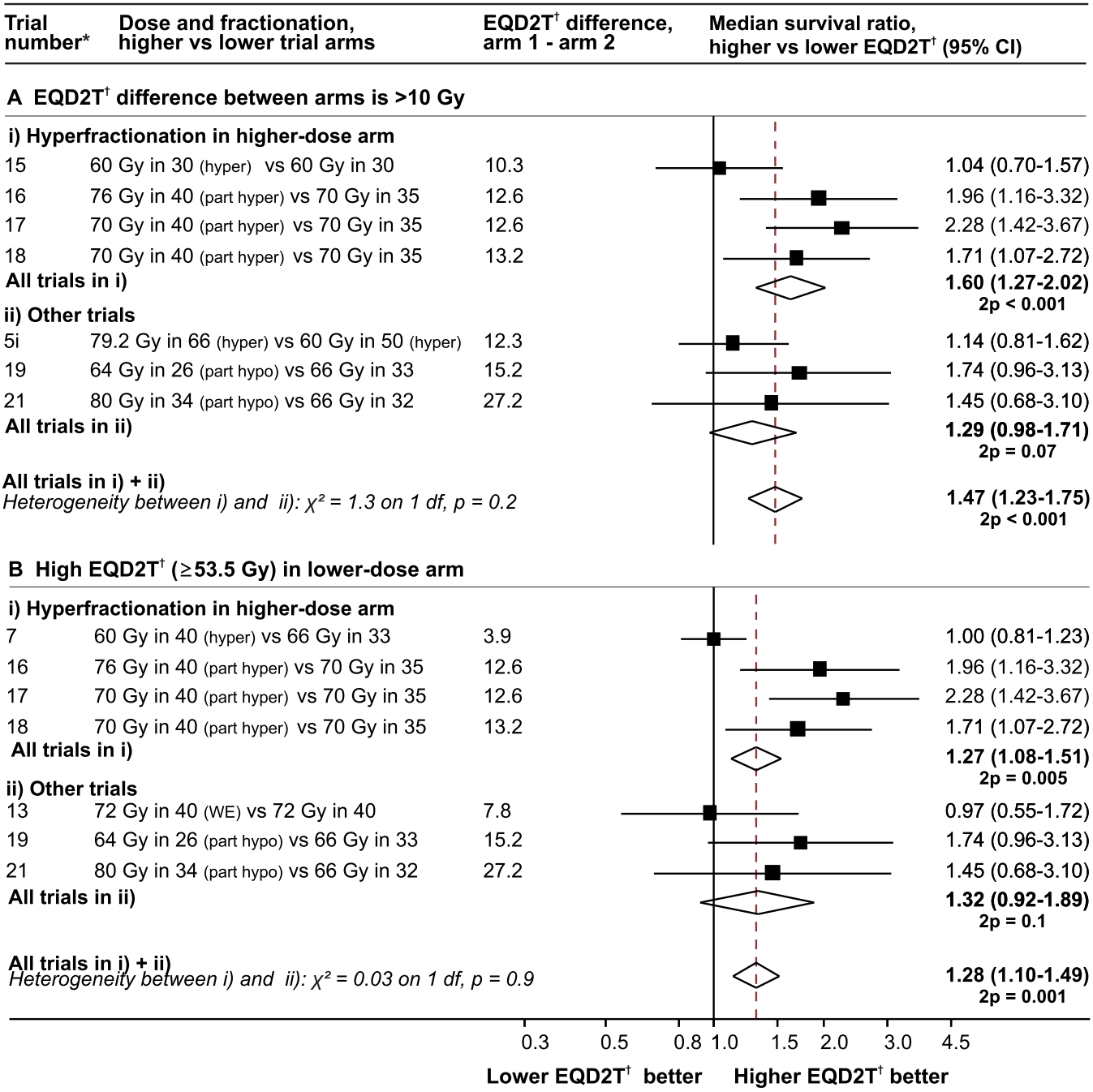
When the 18 radiotherapy-only comparisons were grouped according to dose in the lower-dose arm into three approximately equal sized groups (Figure 2.3, panel B), the median survival ratio, higher versus lower dose, was 1.01 (95% CI 0.89-1.14, p=0.9) for comparisons where the EQD2T in the lower-dose arm was <49.5 Gy, while for comparisons in which it was 49.5-53.4 Gy the median survival ratio was 1.17 (95% CI 1.02-1.33, p=0.02), and for comparisons in which it was ≥53.5 Gy it was 1.28 (95% CI 1.10-1.49, p<0.002). So, surprisingly, the median survival ratio increased progressively with increasing EQD2T in the lower-dose arm, with an increasing trend across the three groups (p for trend=0.01). Even for trials with EQD2T ≥53.5 Gy in the lower-dose arm, further dose escalation provided additional improvement in survival. For the five trials in which



Abbreviations: hyper = hyperfractionated (more than one fraction per day); WE = including weekends; split = split-course radiotherapy, minimum 10 day gap; hypo = hypofractionated (more than 2Gy per fraction); part hyper = partially hyperfractionated; part hypo = partially hypofractionated.

*studies are ordered within groups by ascending EQD2T difference between trial arms
† EQD2T is time-corrected equivalent dose in 2 Gy fractions

Figure 2.3: Median survival ratios, higher vs lower corrected radiotherapy dose (EQD2T). Panel (A) categorised by EQD2T difference between arms. Panel (B) categorised by EQD2T in the lowest-dose arm. Trials with chemotherapy excluded.



Abbreviations: hyper = hyperfractionated (more than one fraction per day); WE = including weekends; split = split-course radiotherapy, minimum 10 day gap; hypo = hypofractionated (more than 2Gy per fraction); part hyper = partially hyperfractionated; part hypo = partially hypofractionated.

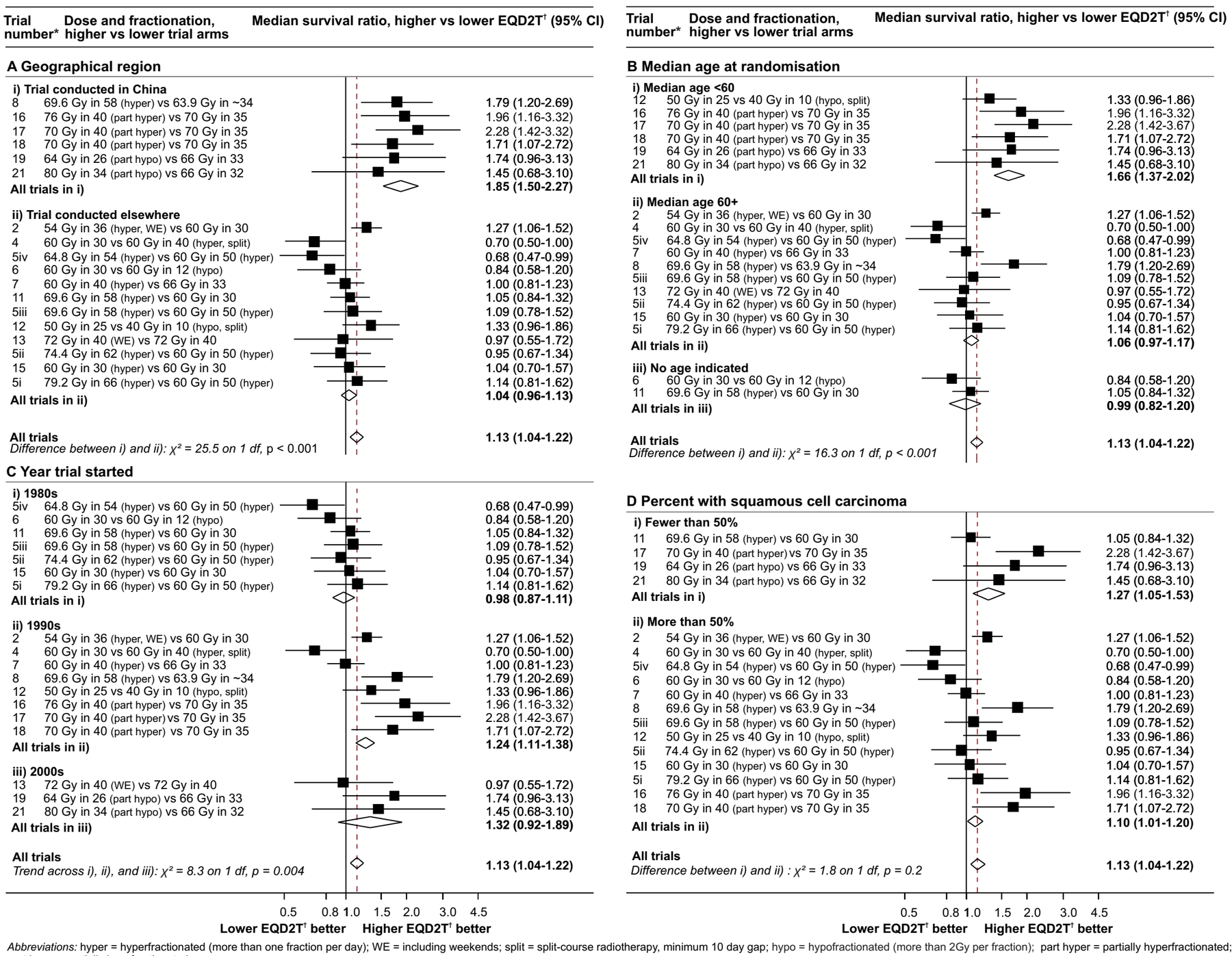
* studies are ordered within groups by ascending EQD2T difference between trial arms
† EQD2T is time-corrected equivalent dose in 2 Gy fractions

Figure 2.4: Median survival ratios, higher vs lower corrected radiotherapy dose (EQD2T), according to whether higher dose was achieved by hyperfractionation or by other means. Panel (A) shows trials with >10Gy EQD2T dose difference between arms (ie, group iii in Fig. 3A). Panel (B) shows trials with EQD2T in the lower-dose arm ≥53.5 Gy (ie, group iii in Fig. B). Trials with chemotherapy excluded.

the dose in the lower-dose arm was ≥53.5 Gy EQD2T and where the dose difference was >10 Gy EQD2T, the median survival ratio was 1.87 (95% CI 1.47-2.38, p<0.001). When comparisons with EQD2T ≥53.5 Gy in the lower-dose arm were categorised into trials in which hyperfractionation was used to escalate dose versus other trials, the median survival ratio for the two groups was similar (1.27, 95% CI 1.08-1.51, and 1.32, 95% CI 0.92-1.89, p for difference=0.9) (Figure 2.4, panel B).

6.3 Heterogeneity between trials and exploratory analyses

Median survival ratios for the 18 radiotherapy-only dose comparisons varied substantially, from 0.68 (95% CI 0.47-0.99) to 2.28 (95% CI 1.42-3.67) (p for heterogeneity <0.001) (Figure 2.2). The difference in EQD2T between trial arms did not account for all the excess heterogeneity, so exploratory analyses were conducted examining the association between median survival ratios and other available factors (Figure 2.5). The median survival ratio, higher versus lower EQD2T, was higher for trials conducted in China compared with trials conducted elsewhere (China: 1.85, 95% CI 1.50-2.27, elsewhere: 1.04, 95% CI 0.96-1.13, p for difference <0.001) (Figure 2.5, panel A), for trials with lower median age (<60 years: 1.66, 95% CI 1.37-2.02, 60+ years: 1.06 95% CI 0.97-1.17, p for difference <0.001 (Figure 2.5, panel B)), and for trials starting more recently (1980s: 0.98, 95% CI 0.87-1.11, 1990s: 1.24, 95% CI 1.11-1.38, 2000s: 1.32, 95% CI 0.92-1.89, p for trend=0.004 (Figure 2.5, panel C)). In contrast, when the trials were grouped according to whether most patients had squamous cell carcinoma (SCC), no significant difference was found (p=0.2) (Figure 2.5, panel D). Geographical region, age, and year trial started were correlated, while percent with squamous cell carcinoma (SCC) was not highly correlated with any other factor (Appendix 1, Table 3). An analysis adjusting for all four factors showed the strongest association between region and median survival ratio (p=0.008), with all other factors non-significant statistically (Appendix 1, Table 4).



Abbreviations: hyper = hyperfractionated (more than one fraction per day); WE = including weekends; split = split-course radiotherapy, minimum 10 day gap; hypo = hypofractionated (more than 2Gy per fraction); part hyper = partially hyperfractionated; part hypo = partially hypofractionated.

*studies are ordered within groups by ascending EQD2T difference between trial arms
† EQD2T is time-corrected equivalent dose in 2 Gy fractions

Figure 2.5: Median survival ratios, higher vs lower corrected radiotherapy dose (EQD2T), according to geographical region (Panel A), median age at randomisation (Panel B), year trial started (Panel C), and percent of patients with squamous cell carcinoma (Panel D). Trials with chemotherapy excluded.

7 Discussion

This large meta-analysis including 3,795 patients in 25 treatment comparisons has, for the first time, brought together all post-1980 randomised evidence comparing different curative intent radiotherapy regimens in NSCLC. To eliminate confounding effects of other treatments, we considered only trials in which other protocol treatments were identical in both arms. We focused on median survival ratios in relation to corrected dose (i.e., time-corrected equivalent dose, EQD2T) differences between trial arms and whether the radiotherapy was given alone or with chemotherapy.

7.1 Radiotherapy without chemotherapy

In 18 trials where no protocol chemotherapy was administered, radiotherapy dose escalation improved overall survival (median survival ratio: 1.13, 95% CI 1.04-1.22), corresponding to a survival gain of approximately two months for patients in these trials. The survival improvement increased progressively as the difference between EQD2T in the two trial arms increased and, in trials where the difference was >10 Gy EQD2T, the median survival ratio was 1.47 (95% CI 1.23-1.75). Remarkably, even for trials where the dose in the lower-dose arm was high (≥53.5 Gy EQD2T), further dose escalation provided additional improvement in survival (median survival ratio: 1.28, 95% CI 1.10-1.49, Figure 2.3, panel B). In trials with ≥53.5 Gy EQD2T in the lower-dose arm where the dose difference exceeded 10 Gy EQD2T, the median survival ratio was 1.87 (95% CI 1.47-2.38), and for these patients the survival gain was approximately one year.

The commonest method of altering dose and fractionation in these trials was hyperfractionation. Two previous meta-analyses of different radiotherapy regimens focused on comparing hyperfractionation or acceleration to conventional radiation, rather than on corrected dose (8, 10). In our study, dose escalation of >10 Gy EQD2T showed a similar improvement in survival regardless of whether it was achieved by hyperfractionation or by other means, suggesting that dose escalation may improve survival regardless of the method used.

Survival improvement from radiotherapy dose escalation was associated with three other factors: younger age, recent trial start date, and whether the trial was conducted in China. The strongest association was for trials conducted in China. Nothing in the trial publications indicated that the Chinese trials differed systematically from other trials and, as the three factors were highly correlated, the geographical association may not be causal. In contrast, it would not be surprising if radiotherapy dose escalation had a greater benefit in younger patients, who may be better able to tolerate radiotherapy than older patients, and thus receive the full prescribed dose. Younger patients may also face a lower risk of death from toxicity than older patients, and have lower competing risks of death from other causes. Survival improvement was also greater in more recent trials. This could be due in part to increased prescribed tumour doses and improved radiotherapy techniques. There was no significant association between dose escalation and the percent of patients with SCC but, for most trials, the percent with SCC was between 40% and 60%, so there was little variation in this factor.

7.2 Radiotherapy with chemotherapy

In trials with concurrent chemotherapy, higher EQD2T led to poorer overall survival, suggesting that risks of increasing radiotherapy dose outweigh benefits when concurrent chemotherapy is given (Figure 2.2.). There was no evidence of heterogeneity in the median survival ratios for trials in this group, but the pooled result was dominated by the RTOG 0617 trial (number 14) in which 207 patients randomised to 58.8 Gy EQD2T (74 Gy in 37 fractions) had higher overall mortality than 217 patients randomised to 49.7 Gy EQD2T (60 Gy in 30 fractions) (HR, higher versus lower dose, 1.38, 95% CI 1.09-1.76, p=0.004); the higher-dose group also had more grade 3 or worse oesophageal toxicity (21% versus 7%, p<0.001) (6). The results of this trial are influencing dose escalation in chemoradiotherapy, as reflected in the 2015 American Society for Therapeutic Radiology (ASTRO) guidelines (7); however, there are arguments why this single trial should not stop further exploration of dose escalation in chemoradiotherapy (41). One of these is that there was reduced protocol adherence in the higher EQD2T arm (higher dose: 153/207 (74%), lower

dose: 180/217 (83%), p=0.02) which may explain the non-significantly increased local failure in the higher-dose group (HR 1.26, 95% CI 0.93-1.71, p=0.1) (6).

Only two trials compared different radiotherapy regimens with the same sequential chemotherapy in both arms. Hence information on dose escalation with sequential chemotherapy is limited.

7.3 Radiotherapy, chemotherapy, and toxicity

The probability of sterilising a tumour increases with increasing tumour radiation dose (42). However, lung cancer radiotherapy inevitably delivers dose to normal lung and adjacent organs that may cause pneumonitis, esophagitis, heart disease, and lung fibrosis (43-45). Adding chemotherapy to radiotherapy further increases toxicity, including myelosuppression, esophagitis (up to six times higher with concurrent chemotherapy), pneumonitis, and treatment-related death (46). Increasing the irradiated volume alongside concurrent chemotherapy can also increase toxicity (47). Toxicity is thus a primary constraint in increasing radiation and chemotherapy dose in NSCLC treatment, especially as patients often have multiple co-morbidities. In this study, it was not possible to analyse the effects of toxicity on median survival due to variability in toxicity reporting across trials in terms of type, severity and time-point.

Modern radiation techniques are being developed to reduce toxicity. These include intensity-modulated radiotherapy, proton beam therapy, and personalised isotoxic radiotherapy, in which patients receive maximal radiotherapy dose based on normal tissue constraints and their individual tumour size and location (48). In future, these efforts to reduce toxicity may facilitate radiotherapy dose escalation, even when chemotherapy is also given.

7.4 Strengths and limitations

Our meta-analysis has several strengths. It is larger and has more power than previously published meta-analyses of trials of curative-intent radiotherapy for lung cancer (8-10). We have, for the first time, examined trials in relation both to the corrected radiotherapy dose and

according to whether chemotherapy was delivered. Most importantly, we have included total treatment time in our dose calculation (EQD2T rather than EQD2). Omitting the time factor would have resulted in substantially different results, as it would have reversed the higher and lower dose arms for 7 trials (numbers 2, 6, 7, 9, 10, 17, and 18) and for two further trials (numbers 13 and 15) the corrected dose would have been identical in the two arms. This is because in seven of these trials, one of the arms was hyperfractionated (more dose-intense) while the other was conventionally fractionated.

The main limitation of our study is a lack of individual patient data. Effects seen at the aggregate level may be weaker or stronger than those examined at the individual level. This also prevented us from considering survival at two years, by which time most patients with occult distant metastases when irradiated would have died. We also could not conduct analyses of deaths from lung cancer versus other causes. Another limitation is that the calculation of EQD2T involves radiobiological assumptions about the way in which radiation kills tumour cells, including values of parameters. For example, in the CHART trial (number 2), 67% of patients in the higher-dose arm versus 34% in the lower-dose arm experienced severe esophagitis, although the EQD2T difference to the tumour was only calculated to be 2.1 Gy (49).

8 Conclusions

Survival in locally advanced NSCLC patients has seen little improvement over forty years (2), so any evidence of improvement in survival is clinically important. Our study shows that when radiotherapy is given without chemotherapy, escalating radiotherapy dose leads to improved survival. This suggests that the optimal radiation dose has yet to be reached, and provides support for further trials of dose escalation, especially with modern radiotherapy techniques that lower toxicity. When chemotherapy is given with radiotherapy, the ability to achieve a cure has, until now, been limited by toxicity, especially when given concurrently. Therefore it may be that the optimal radiation dose for chemoradiotherapy has also not yet been reached in the context of new advances, such as personalised isotoxic dose escalation, and in the continued search for the optimal concurrent chemotherapy regimen. Our study therefore also provides support for consideration of further trials in radiation dose-escalation of chemoradiotherapy for locally advanced NSCLC.

9 Additional Material

9.1 Exclusion of the time factor when calculating EQD2

In this meta-analysis, and throughout this thesis, a time-corrected measure of equivalent dose in 2 Gy fractions was used, rather than the more commonly used EQD2 without time-correction. One of the reviewers of this meta-analysis for the *International Journal of Radiation Oncology, Biology, and Physics* queried whether it was necessary to use a time-correction factor rather than just EQD2. They commented that it could be an additional strength of the paper if it could be shown that the results differed according to whether or not a time-correction is used. There was insufficient space in the publication to include details of such an additional analysis, but they are given here.

In Figure 2.6, the panel on the left is the same as Figure 2.2 in which EQD2T was used to calculate dose and median survival ratios. The panel on the right displays the same results, but using EQD2 without time correction. Trials are displayed in the same order as in the original Figure 2.2, although two trials had to be removed from the EQD2 analysis, as they had the same EQD2 (numbers 13 and 15). In seven trial arm comparisons, the higher and lower-dose arms have switched. The pooled result for trials in which no chemotherapy was given in this EQD2 analysis is now no longer significantly different from one (median survival ratio 0.97, 95% CI 0.90-1.05, p=0.5).

One example of a trial in which the higher- and lower-dose arms switched is the CHART trial (trial number 2), in which CHART is now the lower-dose arm, even though acute and late toxicity in normal tissues was generally higher in the CHART arm than in the conventional arm (49). Other trials in which the arms switched are numbers 6, 7, 9, 10, and, most importantly, 17 and 18. In all of these trial comparisons, one of the arms was either hyperfractionated and accelerated, or hypofractionated, meaning that overall treatment time played an important role in the alteration

Analysis using EQD2T

Trial no.*	Dose and fractionation, higher vs lower trial arms	Median survival ratio, higher vs lower EQD2T† (95% CI)
i) No chemotherapy		
2	54 Gy in 36 (hyper, WE) *vs* 60 Gy in 30	1.27 (1.06-1.52)
4	60 Gy in 30 *vs* 60 Gy in 40 (hyper, split)	0.70 (0.50-1.00)
5iv	64.8 Gy in 54 (hyper) *vs* 60 Gy in 50 (hyper)	0.68 (0.47-0.99)
6	60 Gy in 30 vs 60 Gy in 12 (hypo)	0.84 (0.58-1.20)
7	60 Gy in 40 (hyper) *vs* 66 Gy in 33	1.00 (0.81-1.23)
8	69.6 Gy in 58 (hyper) *vs* 63.9 Gy in ~34	1.79 (1.20-2.69)
11	69.6 Gy in 58 (hyper) *vs* 60 Gy in 30	1.05 (0.84-1.32)
5iii	69.6 Gy in 58 (hyper) *vs* 60 Gy in 50 (hyper)	1.09 (0.78-1.52)
12	50 Gy in 25 *vs* 40 Gy in 10 (hypo, split)	1.33 (0.96-1.86)
13	72 Gy in 40 (WE) *vs* 72 Gy in 40	0.97 (0.55-1.72)
5ii	74.4 Gy in 62 (hyper) *vs* 60 Gy in 50 (hyper)	0.95 (0.67-1.34)
15	60 Gy in 30 (hyper) *vs* 60 Gy in 30	1.04 (0.70-1.57)
5i	79.2 Gy in 66 (hyper) *vs* 60 Gy in 50 (hyper)	1.14 (0.81-1.62)
16	76 Gy in 40 (part hyper) *vs* 70 Gy in 35	1.96 (1.16-3.32)
17	70 Gy in 40 (part hyper) *vs* 70 Gy in 35	2.28 (1.42-3.67)
18	70 Gy in 40 (part hyper) *vs* 70 Gy in 35	1.71 (1.07-2.72)
19	64 Gy in 26 (part hypo) *vs* 66 Gy in 33	1.74 (0.96-3.13)
21	80 Gy in 34 (part hypo) *vs* 66 Gy in 32	1.45 (0.68-3.10)
All trials in i)		**1.13 (1.04-1.22)**
Within-group heterogeneity: χ^2 = 45.8 on 17 df, p < 0.001		**2p = 0.002**
ii) Sequential chemotherapy		
9	57.6 Gy in 36 (hyper) *vs* 64 Gy in 32	1.36 (0.90-2.05)
20	65 Gy in 25 (hypo) *vs* 60 Gy in 30	1.15 (0.65-2.05)
All trials in ii)		**1.29 (0.92-1.80)**
Within-group heterogeneity: χ^2 = 0.2 on 1 df, p = 0.6		**2p = 0.1**
iii) Concurrent chemotherapy		
1ii	68 Gy in 34 (hyper, split) *vs* 67.2 in 56	0.88 (0.57-1.35)
1i	67.2 Gy in 42 (hyper) *vs* 67.2 in 56	0.94 (0.59-1.48)
3	60 Gy in 30 *vs* 60 Gy in 40 (hyper, split)	0.93 (0.70-1.23)
10	60 Gy in 40 (hyper) *vs* 60 Gy in 30	1.20 (0.41-3.46)
14	74 Gy in 37 *vs* 60 Gy in 30	0.71 (0.55-0.90)
All trials in iii)		**0.83 (0.71-0.97)**
Within-group heterogeneity: χ^2 = 3.2 on 4 df, p = 0.5		**2p = 0.02**
All trials in i) + ii) + iii)		**1.07 (1.00-1.15)**
Heterogeneity between i), ii), and iii): χ^2 = 13.4 on 2 df, p = 0.001		**2p = 0.05**

0.3 0.5 0.8 1.0 1.5 2.0 3.0 4.5

Lower EQD2T† better **Higher EQD2T† better**

Abbreviations: hyper = hyperfractionated (more than one fraction per day); WE = including weekends; split = split-course radiotherapy, minimum 10 day gap; hypo = hypofractionated (more than 2Gy per fraction); part hyper = partially hyperfractionated; part hypo = partially hypofractionated.

*studies are ordered within groups by ascending EQD2T difference between trial arms

† EQD2T is time-corrected equivalent dose in 2 Gy fractions

Analysis using EQD2

Trial no.*	Dose and fractionation, higher vs lower trial arms	Median survival ratio, higher vs lower EQD2† (95% CI)
i) No chemotherapy		
2	60 Gy in 30 vs54 Gy in 36 (hyper, WE)	0.79 (0.66-0.94)
4	60 Gy in 30 vs 60 Gy in 40 (hyper, split)	0.70 (0.50-1.00)
5iv	64.8 Gy in 54 vs 60 Gy in 50 (hyper)	0.68 (0.47-0.99)
6	60 Gy in 12 (hypo) vs 60 Gy in 30	1.20 (0.84-1.73)
7	66 Gy in 33 vs 60 Gy in 40 (hyper)	1.00 (0.81-1.23)
8	69.6 Gy in 58 (hyper) vs 63.9 Gy in ~34	1.79 (1.20-2.69)
11	69.6 Gy in 58 (hyper) vs 60 Gy in 30	1.05 (0.84-1.32)
5iii	69.6 Gy in 58 (hyper) vs 60 Gy in 50	1.09 (0.78-1.52)
12	50 Gy in 25 vs 40 Gy in 10 (hyper, split)	1.33 (0.96-1.86)
5ii	74.4 Gy in 62 (hyper) vs 60 Gy in 50 (hyper)	0.95 (0.67-1.34)
5i	79.2 Gy (hyper) in 66 vs 60 Gy in 50 (hyper)	1.14 (0.81-1.62)
16	76 Gy in 40 (part hyper) vs 70 Gy in 35	1.96 (1.16-3.32)
17	70 Gy in 35 vs 70 Gy in 40 (part hyper)	0.44 (0.27-0.70)
18	70 Gy in 35 vs 70 Gy in 40 (part hyper)	0.59 (0.37-0.93)
19	64 Gy in 26 (part hypo) vs 66 Gy in 33	1.74 (0.96-3.13)
21	80 Gy in 34 (part hypo) vs 66 Gy in 32	1.45 (0.68-3.10)
All trials in i)		**0.97 (0.90-1.05)**
Within-group heterogeneity: χ^2 = 54.5 on 15 df, p < 0.001		**2p = 0.5**
ii) Sequential chemotherapy		
9	64 Gy in 32 vs 57.6 Gy in 36 (hyper)	0.73 (0.49-1.11)
20	65 Gy in 25 (hypo) vs 60 Gy in 30	1.15 (0.65-2.05)
All trials in ii)		**0.85 (0.61-1.19)**
Within-group heterogeneity: χ^2 = 1.6 on 1 df, p = 0.2		**2p = 0.4**
iii) Concurrent chemotherapy		
c) Concurrent chemotherapy		
1ii	68 Gy in 34 (hyper, split) vs 67.2 in 56	0.88 (0.57-1.35)
1i	67.2 Gy in 42 (hyper) vs 67.2 in 56	0.94 (0.59-1.48)
3	60 Gy in 30 vs 60 Gy in 40 (hyper, split)	0.93 (0.70-1.23)
10	60 Gy in 30 vs 60 Gy in 40 (hyper)	0.83 (0.29-2.41)
14	74 Gy in 37 vs 60 Gy in 30	0.71 (0.55-0.90)
All trials in iii)		**0.82 (0.70-0.96)**
Within-group heterogeneity: χ^2 = 2.7 on 4 df, p = 0.6		**2p = 0.01**
All trials in i) + ii) + iii)		**0.93 (0.87-1.00)**
Heterogeneity between i), ii), and iii): χ^2 = 3.7 on 2 df, p = 0.2		**2p = 0.05**

0.3 0.5 0.8 1.0 1.5 2.0 3.0 4.5

Lower EQD2† better **Higher EQD2† better**

Abbreviations: hyper = hyperfractionated (more than one fraction per day); WE = including weekends; split = split-course radiotherapy, minimum 10 day gap; hypo = hypofractionated (more than 2Gy per fraction); part hyper = partially hyperfractionated; part hypo = partially hypofractionated.

*studies are ordered within groups by ascending time-corrected EQD2T difference between trial arms (same order as in the published paper)

† EQD2 is equivalent dose in 2 Gy fractions

Figure 2.6: Median survival ratios, higher vs lower corrected radiotherapy dose, according to whether radiotherapy was given without chemotherapy, with sequential chemoradiotherapy, or with concurrent chemoradiotherapy. The left-hand panel is identical to Figure 2.2 and shows corrected radiotherapy dose including a time factor (EQD2T). In the right-hand panel, corrected radiotherapy dose (EQD2) does not include a time factor.

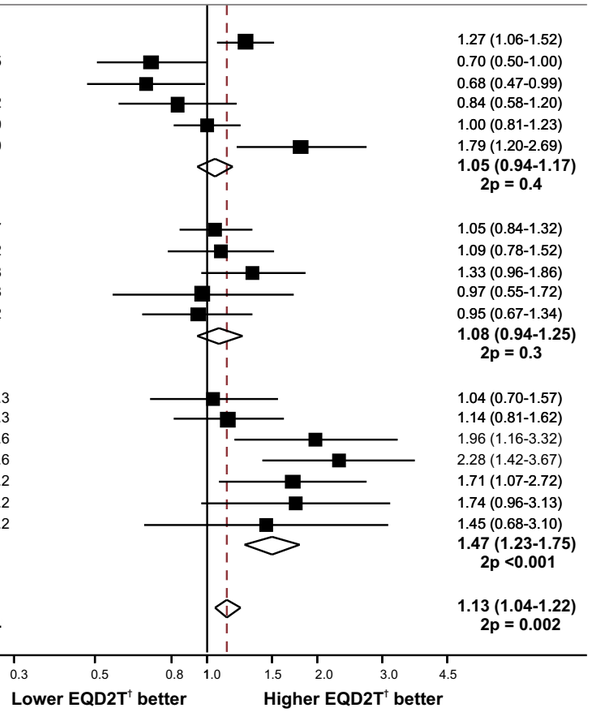
of the fractionation. Trials 17 and 18 had a particularly large difference in dose when calculating EQD2T rather than EQD2, and the individual median survival ratios within these trials were significantly different from one. Whether the hyperfractionated-accelerated arm is the higher- or lower-dose arm in these two studies is therefore an important driver of the overall results. Overall, there were 11 trials in which higher time-corrected dose (EQD2T) was achieved via hyperfractionation. Of these 11 trials, patients experienced greater toxicity in the hyperfractionated-accelerated arm than in the conventional arm in five trials (22, 30, 37, 38, 40). In a further four trials, toxicity in the two arms was comparable, though there was a tendency toward slightly more toxicity in the hyperfractionated-accelerated arm (21, 28, 39, 49). In the final two trials (29, 31), toxicity was similar in the two arms, though in trial 9 there was more oesophagitis in the hyperfractionated-accelerated arm and more pneumonitis in the conventional arm (neither statistically significant) (29). In no trial was there significantly more toxicity in the conventional arm than in the hyperfractionated-accelerated arm.

An analysis of trend across dose difference between trial arms was even more affected by the use of EQD2 rather than EQD2T. This required re-ordering trials in terms of the difference in EQD2, as shown in Figure 2.7. The panel on the left is the original Figure 2.3, panel A, using EQD2T to calculate dose. The panel on the right is the new Figure 2.7, using EQD2. Trials were grouped once again by whether the difference in dose was less than 5 Gy (group i), between 5 and 10 Gy (group ii), and more than 10Gy (group iii). In the new analysis, in group iii there is a slight non-significant benefit of higher dose, but overall there is no trend across increasing dose difference (p for trend=0.7).

An analysis of trend across dose in the lower-dose trial arm was also repeated using EQD2 without time-correction (Figure 2.8). Again, the panel on the left shows the original analysis, the panel on the right the analysis using EQD2 without time-correction. The new analysis did show a trend of benefit as dose in the lower-dose arm increased (Figure 2.8, p for trend=0.02). However, the

Analysis using EQD2T

Trial number*	Dose and fractionation, higher vs lower trial arms	EQD2T†, arm 1 vs arm 2	EQD2T† difference, arm 1 - arm 2	Median survival ratio, higher vs lower EQD2T* (95% CI)
A EQD2T† difference between trial arms				
i) Dose difference <5 Gy				
2	54 Gy in 36 (hyper, WE) vs 60 Gy in 30	51.8 vs 49.7	2.1	1.27 (1.06-1.52)
4	60 Gy in 30 vs 60 Gy in 40 (hyper, split)	49.7 vs 47.2	2.5	0.70 (0.50-1.00)
5iv	64.8 Gy in 54 (hyper) vs 60 Gy in 50 (hyper)	52.3 vs 49.2	3.1	0.68 (0.47-0.99)
6	60 Gy in 30 vs 60 Gy in 12 (hypo)	49.7 vs 46.5	3.2	0.84 (0.58-1.20)
7	60 Gy in 40 (hyper) vs 66 Gy in 33	57.5 vs 53.6	3.9	1.00 (0.81-1.23)
8	69.6 Gy in 58 (hyper) vs 63.9 Gy in ~34	52.3 vs 48.3	4.0	1.79 (1.20-2.69)
All trials in i)				**1.05 (0.94-1.17)**
Within-group heterogeneity: χ^2 = 23.0 on 5 df, p<0.001				**2p = 0.4**
ii) Dose difference 5-10 Gy				
11	69.6 Gy in 58 (hyper) vs 60 Gy in 30	55.4 vs 49.7	5.7	1.05 (0.84-1.32)
5iii	69.6 Gy in 58 (hyper) vs 60 Gy in 50 (hyper)	55.4 vs 49.2	6.2	1.09 (0.78-1.52)
12	50 Gy in 25 vs 40 Gy in 10 (hypo, split)	43.2 vs 36.4	6.8	1.33 (0.96-1.86)
13	72 Gy in 40 (WE) vs 72 Gy in 40	61.3 vs 53.5	7.8	0.97 (0.55-1.72)
5ii	74.4 Gy in 62 (hyper) vs 60 Gy in 50 (hyper)	58.4 vs 49.2	9.2	0.95 (0.67-1.34)
All trials in ii)				**1.08 (0.94-1.25)**
Within-group heterogeneity: χ^2 = 2.3 on 4 df, p = 0.7				**2p = 0.3**
iii) Dose difference >10 Gy				
15	60 Gy in 30 (hyper) vs 60 Gy in 30	60.0 vs 49.7	10.3	1.04 (0.70-1.57)
5i	79.2 Gy in 66 (hyper) vs 60 Gy in 50 (hyper)	61.5 vs 49.2	12.3	1.14 (0.81-1.62)
16	76 Gy in 40 (part hyper) vs 70 Gy in 35	68.8 vs 56.2	12.6	1.96 (1.16-3.32)
17	70 Gy in 40 (part hyper) vs 70 Gy in 35	68.8 vs 56.2	12.6	2.28 (1.42-3.67)
18	70 Gy in 40 (part hyper) vs 70 Gy in 35	68.8 vs 55.6	13.2	1.71 (1.07-2.72)
19	64 Gy in 26 (part hypo) vs 66 Gy in 33	68.8 vs 53.6	15.2	1.74 (0.96-3.13)
21	80 Gy in 34 (part hypo) vs 66 Gy in 32	80.8 vs 53.6	27.2	1.45 (0.68-3.10)
All trials in iii)				**1.47 (1.23-1.75)**
Within-group heterogeneity: χ^2 = 10.0 on 6 df, p = 0.1				**2p <0.001**
All trials in i) + ii) + iii)				**1.13 (1.04-1.22)**
Test for trend across i), ii), and iii): χ^2 = 8.2 on 1 df, p = 0.004				**2p = 0.002**

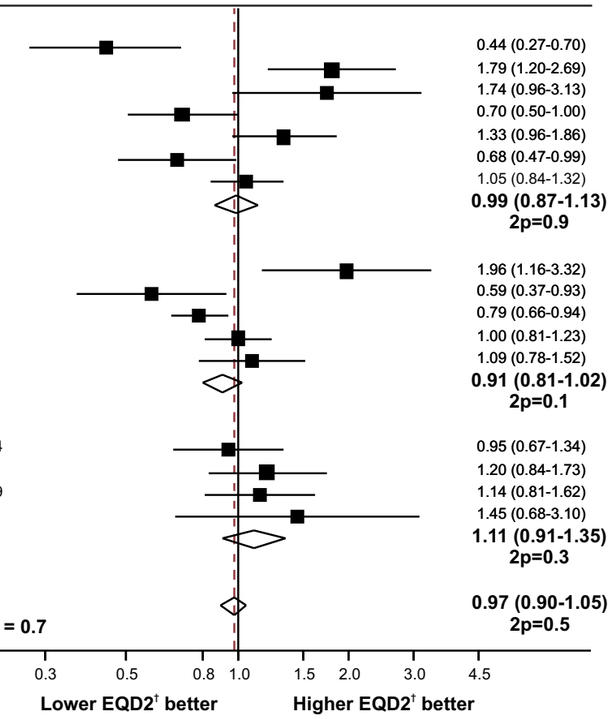


Abbreviations: hyper = hyperfractionated (more than one fraction per day); WE = including weekends; split = split-course radiotherapy, minimum 10 day gap; hypo = hypofractionated (more than 2Gy per fraction); part hyper = partially hyperfractionated; part hypo = partially hypofractionated.

*studies are ordered within groups by ascending EQD2T difference between trial arms
†EQD2T is time-corrected equivalent dose in 2 Gy fractions

Analysis using EQD2

Trial number*	Dose and fractionation, higher vs lower trial arms	EQD2†, arm 1 vs arm 2	EQD2† difference, arm 1 - arm 2	Median survival ratio, higher vs lower EQD2* (95% CI)
A EQD2† difference between trial arms				
i) Dose difference <5 Gy				
17	70 Gy in 40 (part. hyper) vs 70 Gy in 35	68.8 vs 56.2	1.2	0.44 (0.27-0.70)
8	69.6 Gy in 58 vs 63.9 Gy in ~34	52.3 vs 48.3	1.9	1.79 (1.20-2.69)
19	64 Gy in 26 vs 66 Gy in 33	68.8 vs 53.6	2	1.74 (0.96-3.13)
4	60 Gy in 30 vs 60 Gy in 40 (split)	49.7 vs 47.2	2.5	0.70 (0.50-1.00)
12	50 Gy in 25 vs 40 Gy in 10 (split)	43.2 vs 36.4	3.3	1.33 (0.96-1.86)
5iv	64.8 Gy in 54 vs 60 Gy in 50	52.3 vs 49.2	4.5	0.68 (0.47-0.99)
11	69.6 Gy in 58 vs 60 Gy in 30	55.4 vs 49.7	5	1.05 (0.84-1.32)
All trials in i)				**0.99 (0.87-1.13)**
Within-group heterogeneity: χ^2 = 34.0 on 6 df, p<0.001				**2p=0.9**
ii) Dose difference 5-10 Gy				
16	76 Gy in 40 vs 70 Gy in 35	68.8 vs 56.2	5.4	1.96 (1.16-3.32)
18	70 Gy in 40 (part. hyper) vs 70 Gy in 35	68.8 vs 55.6	5.6	0.59 (0.37-0.93)
2	60 Gy in 30 vs54 Gy in 36	60.0 vs 51.8	8.2	0.79 (0.66-0.94)
7	60 Gy in 40 vs 66 Gy in 33		8.5	1.00 (0.81-1.23)
5iii	69.6 Gy in 58 vs 60 Gy in 50	55.4 vs 49.2	9	1.09 (0.78-1.52)
All trials in ii)				**0.91 (0.81-1.02)**
Within-group heterogeneity: χ^2 = 16.1 on 4 df, p=0.003				**2p=0.1**
iii) Dose difference >10 Gy				
5ii	74.4 Gy in 62 vs 60 Gy in 50	58.4 vs 49.2	13.4	0.95 (0.67-1.34)
6	60 Gy in 30 vs 60 Gy in 12		15	1.20 (0.84-1.73)
5i	79.2 Gy in 66 vs 60 Gy in 50	61.5 vs 49.2	17.9	1.14 (0.81-1.62)
21	80 Gy in 34 vs 66 Gy in 32	80.8 vs 53.6	19	1.45 (0.68-3.10)
All trials in iii)				**1.11 (0.91-1.35)**
Within-group heterogeneity: χ^2 = 1.5 on 3 df, p=0.7				**2p=0.3**
All trials in i) + ii) + iii)				**0.97 (0.90-1.05)**
Test for trend across i), ii), and iii): χ^2 = 0.2 on 1 df, p = 0.7				**2p=0.5**



Abbreviations: hyper = hyperfractionated (more than one fraction per day); WE = including weekends; split = split-course radiotherapy, minimum 10 day gap; hypo = hypofractionated (more than 2Gy per fraction); part hyper = partially hyperfractionated; part hypo = partially hypofractionated.

*studies are ordered within groups by ascending EQD2 difference between trial arms
†EQD2 is equivalent dose in 2 Gy fractions, not corrected for time

Figure 2.7: Median survival ratios, higher vs lower corrected radiotherapy dose, categorised by dose difference between arms. Trials with chemotherapy are excluded. The left-hand panel is identical to Figure 2.3, Panel A, and shows corrected radiotherapy dose including a time factor (EQD2T). In the right-hand panel, corrected radiotherapy dose (EQD2) does not include a time factor.

Analysis using EQD2T

Trial number*	Dose and fractionation, higher vs lower trial arms	EQD2T†, arm 1 vs arm 2	EQD2T† difference, arm 1 - arm 2	Median survival ratio, higher vs lower EQD2T* (95% CI)
B	**EQD2T† in lower-dose arm**			
	i) Low dose (<49.5 Gy)			
4	60 Gy in 30 vs 60 Gy in 40 (hyper, split)	49.7 vs 47.2	2.5	0.70 (0.50-1.00)
5iv	64.8 Gy in 54 (hyper) vs 60 Gy in 50 (hyper)	52.3 vs 49.2	3.1	0.68 (0.47-0.99)
6	60 Gy in 30 vs 60 Gy in 12 (hypo)	49.7 vs 46.5	3.2	0.84 (0.58-1.20)
8	69.6 Gy in 58 (hyper) vs 63.9 Gy in ~34	52.3 vs 48.3	4.0	1.79 (1.20-2.69)
5iii	69.6 Gy in 58 (hyper) vs 60 Gy in 50 (hyper)	55.4 vs 49.2	6.2	1.09 (0.78-1.52)
12	50 Gy in 25 vs 40 Gy in 10 (hypo, split)	43.2 vs 36.4	6.8	1.33 (0.96-1.86)
5ii	74.4 Gy in 62 (hyper) vs 60 Gy in 50 (hyper)	58.4 vs 49.2	9.2	0.95 (0.67-1.34)
5i	79.2 Gy in 66 (hyper) vs 60 Gy in 50 (hyper)	61.5 vs 49.2	12.3	1.14 (0.81-1.62)
	All trials in i)			**1.01 (0.89-1.14)**
	Within-group heterogeneity: χ^2 = 20.7 on 7 df, p = 0.004			**2p = 0.9**
	ii) Medium dose (49.5-53.4 Gy)			
2	54 Gy in 36 (hyper, WE) vs 60 Gy in 30	51.8 vs 49.7	2.1	1.27 (1.06-1.52)
11	69.6 Gy in 58 (hyper) vs 60 Gy in 30	55.4 vs 49.7	5.7	1.05 (0.84-1.32)
15	60 Gy in 30 (hyper) vs 60 Gy in 30	60.0 vs 49.7	10.3	1.04 (0.70-1.57)
	All trials in ii)			**1.17 (1.02-1.33)**
	Within-group heterogeneity: χ^2 = 2.0 on 2 df, p = 0.4			**2p = 0.02**
	iii) High dose (≥53.5 Gy)			
7	60 Gy in 40 (hyper) vs 66 Gy in 33	57.5 vs 53.6	3.9	1.00 (0.81-1.23)
13	72 Gy in 40 (WE) vs 72 Gy in 40	61.3 vs 53.5	7.8	0.97 (0.55-1.72)
16	76 Gy in 40 (part hyper) vs 70 Gy in 35	68.8 vs 56.2	12.6	1.96 (1.16-3.32)
17	70 Gy in 40 (part hyper) vs 70 Gy in 35	68.8 vs 56.2	12.6	2.28 (1.42-3.67)
18	70 Gy in 40 (part hyper) vs 70 Gy in 35	68.8 vs 55.6	13.2	1.71 (1.07-2.72)
19	64 Gy in 26 (part hypo) vs 66 Gy in 33	68.8 vs 53.6	15.2	1.74 (0.96-3.13)
21	80 Gy in 34 (part hypo) vs 66 Gy in 32	80.8 vs 53.6	27.2	1.45 (0.68-3.10)
	All trials in iii)			**1.28 (1.10-1.49)**
	Within-group heterogeneity: χ^2 = 17.0, p = 0.009			**2p = 0.001**
	All in trials in i) + ii) + iii)			**1.13 (1.04-1.22)**
	Test for trend across i), ii), and iii): χ^2 = 6.0 on 1 df, p = 0.01			**2p = 0.002**

0.3 0.5 0.8 1.0 1.5 2.0 3.0 4.5

Lower EQD2T† better **Higher EQD2T† better**

Abbreviations: hyper = hyperfractionated (more than one fraction per day); WE = including weekends; split = split-course radiotherapy, minimum 10 day gap;hypo = hypofractionated (more than 2Gy per fraction); part hyper = partially hyperfractionated; part hypo = partially hypofractionated.

*studies are ordered within groups by ascending EQD2T difference between trial arms
† EQD2T is time-corrected equivalent dose in 2 Gy fractions

Analysis using EQD2

Trial number*	Dose and fractionation, higher vs lower trial arms	EQD2†, arm 1 vs arm 2	EQD2† difference, arm 1 - arm 2	Median survival ratio, higher vs lower EQD2* (95% CI)
B	**EQD2† in lower-dose arm**			
	i) Low dose (<49.5 Gy)			
12	50 Gy in 25 vs 40 Gy in 10 (split)	43.2 vs 36.4	3.3	1.33 (0.96-1.86)
5iv	64.8 Gy in 54 vs 60 Gy in 50	52.3 vs 49.2	4.5	0.68 (0.47-0.99)
2	60 Gy in 30 vs54 Gy in 36	60.0 vs 51.8	8.2	0.79 (0.66-0.94)
	All trials in i)			**0.85 (0.74-0.99)**
	Within-group heterogeneity: χ^2 = 9.2 on 2 df, p=0.01			**2p=0.03**
	ii) Medium dose (49.5-53.4 Gy)			
4	60 Gy in 30 vs 60 Gy in 40 (split)	49.7 vs 47.2	2.5	0.70 (0.50-1.00)
7	60 Gy in 40 vs 66 Gy in 33		8.5	1.00 (0.81-1.23)
5iii	69.6 Gy in 58 vs 60 Gy in 50	55.4 vs 49.2	9	1.09 (0.78-1.52)
5ii	74.4 Gy in 62 vs 60 Gy in 50	58.4 vs 49.2	13.4	0.95 (0.67-1.34)
5i	79.2 Gy in 66 vs 60 Gy in 50	61.5 vs 49.2	17.9	1.14 (0.81-1.62)
	All trials in ii)			**0.97 (0.85-1.11)**
	Within-group heterogeneity: χ^2 = 4.7 on 4 df, p=0.3			**2p=0.7**
	iii) High dose (≥53.5 Gy)			
17	70 Gy in 40 (part. hyper) vs 70 Gy in 35	68.8 vs 56.2	1.2	0.44 (0.27-0.70)
8	69.6 Gy in 58 vs 63.9 Gy in ~34	52.3 vs 48.3	1.9	1.79 (1.20-2.69)
19	64 Gy in 26 vs 66 Gy in 33	68.8 vs 53.6	2	1.74 (0.96-3.13)
11	69.6 Gy in 58 vs 60 Gy in 30	55.4 vs 49.7	5	1.05 (0.84-1.32)
16	76 Gy in 40 vs 70 Gy in 35	68.8 vs 56.2	5.4	1.96 (1.16-3.32)
18	70 Gy in 40 (part. hyper) vs 70 Gy in 35	68.8 vs 55.6	5.6	0.59 (0.37-0.93)
6	60 Gy in 30 vs 60 Gy in 12		15	1.20 (0.84-1.73)
21	80 Gy in 34 vs 66 Gy in 32	80.8 vs 53.6	19	1.45 (0.68-3.10)
	All trials in iii)			**1.09 (0.95-1.26)**
	Within-group heterogeneity: χ^2 = 34.9 on 7 df, p<0.001			**2p=0.2**
	All trials in i) + ii) + iii)			**0.97 (0.90-1.05)**
	Test for trend across i), ii), and iii): χ^2 = 5.8 on 1 df, p = 0.02			**2p=0.5**

0.3 0.5 0.8 1.0 1.5 2.0 3.0 4.5

Lower EQD2† better **Higher EQD2† better**

Abbreviations: hyper = hyperfractionated (more than one fraction per day); WE = including weekends; split = split-course radiotherapy, minimum 10 day gap; hypo = hypofractionated (more than 2Gy per fraction); part hyper = partially hyperfractionated; part hypo = partially hypofractionated.

*studies are ordered within groups by ascending EQD2 difference between trial arms
† EQD2 is equivalent dose in 2 Gy fractions, not corrected for time

Figure 2.8: Median survival ratios, higher vs lower corrected radiotherapy dose, categorised by EQD2T in the lowest-dose arm. Trials with chemotherapy are excluded. The left-hand panel is identical to Figure 2.3, Panel B, which shows corrected radiotherapy dose including a time factor (EQD2T). In the right-hand panel, corrected radiotherapy dose (EQD2) does not include a time factor.

values of pooled median survival ratios within groups i, ii, and iii were shifted toward the null (panel on the right) as compared to the same analysis including the time factor (panel on the left).

9.2 Conclusions on use of the time factor

Including or excluding a time factor in the calculation of dose equivalence affected the results and conclusions of this meta-analysis. The individual trial comparisons that were most affected were those that used hyperfractionation and acceleration versus conventional daily fractionation. If the reduced time over which the hyperfractionated-accelerated regimens was given was not taken into account, some of these regimens appeared to be lower-dose. However, based on toxicity to normal surrounding tissues, it is probable that the hyperfractionated-accelerated regimens were in fact higher-dose regimens and that it is therefore appropriate to include a time factor when calculating dose equivalence. The formula used in this study was first published in 1989 (50). This is increasingly considered the standard, but formulae without the time-correction are still widely used.

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Chapter 3

Developing a cohort study: finding a dataset, overcoming challenges

1 Finding a dataset

Having explored the literature (Chapter 1), it was evident that the diverse radiotherapy fractionation practices in the UK would be an excellent opportunity for research, if appropriate data could be found to conduct a study. In the first months of the DPhil, autumn 2012, radiation oncologists practicing in the UK were consulted as well as members of the National Cancer Intelligence Network, in order to determine whether and where such data might be found. Online searches showed that an initiative had begun in 2009 to collect radiotherapy data across the UK, the Radiotherapy Dataset (RTDS). However, these consultations revealed that RTDS data had been difficult to collect in the first few years and that it was only around 2011-2012 that data were becoming usable. Other than limited variables available for some geographic areas, the dataset was not yet ready for release and it would be several more years until it would be.

In a separate meeting with the local Oxford Cancer Registry Office, then the Oxford Cancer Intelligence Unit (OCIU), an initiative was identified just within the Oxford and Trent registry catchment areas to collect data on radiotherapy fractions received by patients. Dr. Ken Lloyd, former clinical oncologist at Northampton General Hospital, had developed this project and was careful in the collection and quality checking of these data, especially in Oxford, where the project began in the year 1999. The dataset was called Clinical Information Analysis (CIA). The CIA project ended in 2010 because of the new RTDS: double data collection was an unnecessary burden on the Oxford and Trent hospitals. However, the CIA served as a regional pilot and helped to inform which data items could be collected both in the RTDS and later also the Systemic Anticancer Treatment dataset (SACT). The OCIU Director, Dr. Monica Roche, was keen to support using these data for this DPhil research as the CIA data had up to that point not been analysed. One descriptive tabulation of number of fractions for breast cancer had been presented at a conference (1), but no other publications using these data had been produced. The only other uses of this dataset were internal to the NHS, including reports on radiotherapy treatment patterns by cancer site and verification of routine cancer registrations.

The OCIU were able to provide a crude tabulation of aggregated numbers of fractions by cancer site. There seemed to be substantial variability within most cancer sites in numbers of fractions given. This initial tabulation of all CIA data is available in Table 3.1. Given the variability in fractionation, it was decided to pursue using these data for this DPhil.

The next steps in obtaining these data were to write a study protocol, obtain ethical approval, obtain approval from the NHS to use these data, and collaborate with the OCIU to produce a dataset that could be sent to the University of Oxford for analysis. Writing the study protocol was straightforward (Appendix 2). The OCIU were helpful in providing information about other data sources also available within the cancer registration system, and it was possible to conceive of a dataset including many potentially confounding factors.

Table 3.1: Initial dataset: Number of patients receiving each number of radiotherapy fractions, by cancer site

No. fractions	Breast/ DCIS	Lung	Head and Neck	Brain and CNS	Upper GI	Colorectal	Urological	Gynaecological	Haematological	Bone/ cartilage	Skin	Other	Benign	Undefined	Total
0	15	7	3	2	1	3	6		1		8				**46**
1	2,244	2,546	696	57	421	421	3,705	401	874	110	253	424	55	1,512	**13,719**
2	152	717	12	33	32	55	137	212	62	12	48	35	2	9	**1,518**
3	372	449	12	9	27	43	322	263	53	11	101	14	1		**1,677**
4	143	95	14	12	34	28	90	59	48	8	69	31	2	2	**635**
5	1,956	2,403	205	76	1,334	979	1,870	190	542	118	1,187	407	5	31	**11,303**
6	124	69	95	162	63	33	39	5	59	5	120	23	1	4	**802**
7	16	12	10	6	4	1	19	6	13	1	19				**107**
8	28	56	8	6	3	10	51	12	5	3	36	3	1		**222**
9	16	14	10	2	2	8	9	7	9	1	103	2			**183**
10	280	334	114	29	202	170	213	130	168	40	334	64	4	13	**2,095**
11	21	11	9	1	2	4	7	1	5	1	5	3		18	**88**
12	473	252	17	13	10	22	30	8	77	6	8	9	1	2	**928**
13	1,766	66	9	6	1	3	18	8	2		7				**1,886**
14	17	4	5	1	2	5	7	5	6	2	1	7			**62**
15	2,891	225	49	6	24	26	68	41	255	16	101	15	1	3	**3,721**
16	979	4	1	4	1	4	10	5	6		1	1			**1,016**
17	28	5	6	4	1	8	17	3	74		3	1			**150**
18	1,392	18	22	5	9	11	33	5	87	2	2	1		2	**1,589**
19	42	10	6	2	2	5	161	3	11	1	1	1			**245**
20	2,707	321	368	28	48	34	2,208	103	284	28	81	9	6	13	**6,238**
21	13	7	2	4	1	3	6	2	2						**40**
22	15	2	3	3	3	8		9	17	2	1	1			**64**
23	151	4	2	3	2	7	19	6	8	3	1	1			**207**
24	29		4		1	12	4	8		2		2			**62**
25	2,053	60	78	48	223	983	80	731	32	46	23	90	26	6	**4,479**
26	16	5		3	3	8		7		2					**44**
27	17	9	11	2	3	12	8	77	3	5	1				**148**
28	95	4	8	26	51	431	17	188	4	9	4	3	2	1	**843**
29	26	3	12	5	1	7	4	9			4				**71**
30	917	57	624	612	9	65	64	49	3	84	73	38	4	7	**2,606**
31	16	5	12	21	1	2	10	5		6		1			**79**
32	10	32	71	16	6	5	338	11	1	22	11	5		1	**529**
33	12	22	432	14	8	1	127	34	2	78	17	10	1	3	**761**
34		2	15	1			14	17	1	2		1			**53**
35	3	3	31	1			622	17	1	2		2		2	**684**
36	2	137	7	1			14	9	1	2	3				**176**
37	3	1	2	2	1	1	619	6		1					**636**
38	1		2				7	4							**14**
39			7				3	1			1				**12**
40		1	3					1							**5**
42			1												**1**
43	1														**1**
44	1			1											**2**
45			1												**1**
49										1					**1**
50					1										**1**
67	1														**1**
75			1												**1**
Missing	4,192	1,680	625	217	447	704	2,756	603	656	108	653	394		724	**13,759**
Total	**23,236**	**9,652**	**3,625**	**1,444**	**2,984**	**4,122**	**13,732**	**3,261**	**3,372**	**740**	**3,280**	**1,598**	**112**	**2,353**	**73,511**

2 The first hurdle: ethical approval

Difficulties began with the ethical approval process. Over the past decade, accessing any data through the NHS has become increasingly difficult, with more regulations in place and greater concern for patient data protection. Consequently, the OCIU would not permit any use of individual patient data unless ethical approval had been obtained, even if these data were anonymised and patients never contacted. However, the NHS Research Ethics Service had as a guideline that studies involving anonymised data would not require ethical approval. Any NHS ethical approval process required the sponsorship of the study by an institution with a research office. In the case of Clinical Trial Service Unit, where this study group is based, this is the Research and Development Office at Oxford University Hospitals. The team at that office were perplexed about this request for ethics approval, and a special exception had to be negotiated to permit this study to be ethically reviewed and to be sponsored by Oxford University Hospitals. By the time both of these endorsements had been obtained, one year and three months of the DPhil had elapsed.

3 The second hurdle: massive changes to the English cancer registration system

During the lengthy process of obtaining ethical approval, the OCIU was completely transformed. Since the beginning of UK cancer registration in the 1970s, there had been eight separate cancer registries in England, as well as additional registries in Wales, Scotland, and Northern Ireland. In England, there was the requirement that cancer registries collect a mandatory minimum dataset, including cancer site, basic demographics, date of diagnosis, and whether any radiotherapy, chemotherapy, or surgery had been received. Only primary cancers were to be recorded, not cancer recurrences. No further details of treatment were required. However, the individual registries each had their own system for how such data were obtained, quality-assured and recorded, and most had many more pieces of information they collected systematically. Over time, each of the registries developed their own area of expertise. For instance, the OCIU was especially interested in collecting details on head and neck cancers, while the West Midlands specialised in breast cancer.

In 2008, the National Cancer Intelligence Network (NCIN) was formed, in preparation for the separation of cancer registration from the National Health Service (NHS). Cancer registration would be part of the new Public Health England (PHE), an effort to remove public health from the NHS as part of an NHS restructure. The NCIN was tasked with designing a single, centrally managed cancer registration system for England, bringing together these eight different registries. Together with the Office of National Statistics (ONS), a new registration system was developed called the English Online Registration Environment (ENCORE).

In 2013, the new PHE took effect, all data from the eight registries were fully moved to the new ENCORE, and the system went live. As part of this move, many jobs were cut and systems changed. With fewer data analysis staff left, it appeared for some time that this study would no

longer be possible. With some persistence, it was agreed it could be possible for the study to proceed if I conducted most data management at PHE myself.

3.1 Accessing the data

As the new PHE needed to develop a uniform system not only for data collection but also for every other institutional matter, it was difficult to pursue the two parallel tasks that now needed to be accomplished: securing a student placement agreement and obtaining permission to access data. As the new PHE was being developed, it was unclear who was responsible for making decisions, and new forms were in the process of being created. However, the former OCIU director continued to be instrumental in pushing forward this project. Data access was finally obtained in March 2014, one and a half years after the start of the DPhil. During this period, most of the work on the meta-analysis of non-small cell lung cancer trials was undertaken (Chapter 2).

3.2 Challenges in the data

The data sources used in this study are described in Chapter 4. The first dataset used was the Oxford CIA, to which data were added from the Cancer Analysis System (CAS), Cancer Waiting Times, Indices of Multiple Deprivation, a subset of the Trent CIA, Oxford Hospital Data, breast cancer recurrence, and finally Hospital Episodes Statistics (HES). CAS is the analytical data version of ENCORE and includes information from several other PHE datasets (see Chapter 4 for full details, especially Figure 4.1).

The Oxford CIA dataset had been carefully managed under the auspices of Dr. Ken Lloyd, and it was possible to begin work on this dataset directly. The data were not incorporated into the new PHE Cancer Analysis System (CAS), as they were only local. They had been untouched for several years, and all analysts who had worked with these data were now gone. The principal challenge in managing CIA data was a high proportion of missing NHS numbers. It was necessary to discard the first five years of data collection altogether (1999-2003), during which NHS numbers and other

identifiers (names, dates of birth) had not been not systematically collected. While waiting for data access, a colleague at PHE undertook tracing NHS numbers for 19,248 patients treated between 2004 and 2011. After identifying all eligible patients in the CIA data, 1,008 patients remained without NHS numbers. It was possible to manually trace all but 252 of these.

At the time of developing the study protocol, most of the variables listed as being necessary for analysis were in fact to come from the National Cancer Data Repository, which was now no longer in use. As new data for follow-up information were needed, data from the new CAS were used for this project instead. Old data had been migrated to this new system, coming from the eight former cancer registries. This data migration, as well as data duplications that had not yet been processed in the old datasets, resulted in many anomalies in CAS that would take two to three years to rectify. Some of the variables in the former dataset were now somewhat different or unavailable.

4 The third hurdle: data collation

When CIA data were ready to be merged with CAS data, the data anomalies in the new CAS system resulted in many patients having multiple records in CAS that could not all be systematically eliminated. The multiple records were difficult to manage because many patients have multiple cancers, so many of the records were genuine, but many were not. An additional challenge in this merge between CIA and CAS data was that CAS uses the useful system of tumour identifiers, making it possible to distinguish between different cancers for the same person. However, the CIA data only used NHS numbers, which are unique to a person but not to a tumour. It was necessary to undertake a difficult process of matching radiotherapy information in CIA with the correct tumour information in CAS using dates and cancer sites (see Chapter 4, especially Figure 4.2).

Though PHE data work had commenced in March, 2014, the data were only ready to begin analyses January, 2017. One year of this delay can be explained by the successful publication of the meta-analysis (2) and by six months of maternity leave. The remaining year and three-quarters were spent on PHE data management.

5 The fourth hurdle: missing data

It was known from the outset that cancer stage was poorly recorded within the cancer registration system and information on recurrence, comorbidity, and smoking status was not available[1]. From working with the data, it became clear that other important fields were also missing for a high proportion of patients, in particular underlying cause of death and surgical treatment.

During 2015, colleagues from the CTSU had begun another collaboration with PHE to develop a national breast recurrence algorithm, using data from multiple sources to derive whether patients developed a recurrence, metastasis, contralateral breast cancer, or death due to breast cancer (Gurdeep Mannu, personal communication). In 2016, PHE colleagues working on this algorithm were able to provide better stage for breast cancer patients. They were also able to obtain surgical information directly from Hospital Episodes Statistics (HES) data for all invasive breast cancer (BC) and ductal carcinoma in situ (DCIS) patients in the study, reducing the proportion missing these data from 20% to 11%; for Leicester patients, the proportions missing went from 99% to 17%. Finally, though the recurrence algorithm is not yet ready for widespread use, it was possible to use it for this DPhil, enabling much more powerful analyses for invasive BC.

For lung cancer, an attempt was made to overcome the hurdle of important missing information by conducting a sub-study in Oxford to examine patient notes. It was possible to obtain good information for most Oxford lung patients on stage, comorbidity, smoking status, and timing of chemotherapy relative to radiotherapy (further details in Chapter 4).

[1] A Charlson comorbidity index based on HES was created from 2006 onwards, but this was found not to be useful as very few patients had a record of any comorbidity.

6 The fifth hurdle: hospital data identifiers

The study protocol included incorporation of data directly obtained from hospitals, so that information on late effects of radiotherapy could be added to the dataset (Appendix 2). For example, information on fibrosis after radiotherapy might have been obtained from pathology tissue biopsies. Late effects would have been especially useful for cancers with good survival, for which late effects are a bigger problem than for cancers with poorer survival. More events could have been obtained for analyses, rather than just using survival as an end point.

Permission was obtained from all potential treatment centres in the study (Oxford and Trent catchment areas) by writing to relevant hospital departmental directors, so that this part of the study could be commenced directly after obtaining access to PHE data. This process required coordination between PHE and contacts at each hospital, as letters were sent in the name of PHE.

Once PHE data were available and a final dataset of eligible CIA patients in Oxford had been produced, a first task was to determine whether it was possible to link these data to data held at Oxford University Hospitals. After contact with several departments there, a pilot was conducted with histopathology data, as the data held there seemed promising and staff were amenable to such a project.

It materialised that NHS numbers were only available for 30% of pilot data and using other identifiers (names, dates of birth) only resulted in a 60% match overall. The issue of missing identifiers was not resolved in time for the DPhil. This effort had required a lot of manual data matching, and it was decided that pursuing such a strategy for tens of thousands of patients would be too big a task. Such an effort would need to be repeated in the other departments at the hospital, and again at all of the other hospitals, each of which stores data differently.

This issue highlights the drawbacks of having different identifiers hospital by hospital, with some patients carrying multiple identifiers if they are treated at multiple hospitals. If there is no central

database within a hospital that links NHS number to hospital identifiers, then much information is lost. It became apparent from the pilot merge with histopathological data that NHS numbers were not missing at random, but that patients who were referred to Oxford University Hospitals from another hospital were more likely to have missing identifiers.

7 Lessons learned

7.1 Break problems down into multiple smaller tasks

In this project, this lesson applied especially to data cleaning work, big data merges with new data, and assessing feasibility of hospital data use.

For cancer data management, it is important to work on cancer sites separately, whether that be preparing and conducting analyses, or whether that is data cleaning work. Each cancer site has specific attributes and often errors in the data differ and mean different things for different sites. When deduplicating CAS data, working through each cancer site separately facilitated detection of repeating patterns and made each task more manageable.

Similarly, when attempting to obtain new data, pilots of about 100 patients are good to check whether problems may arise that need resolving prior to attempting a merge. This was especially helpful when trying to obtain histopathological records at Oxford University Hospitals using NHS number as the linking identifier. The pilot enabled the decision not to use these data before much time had been invested.

A second helpful pilot merge with a new data source was an initial merge of CIA and CAS data. A first merge of only identifiable data and a small number of other variables was conducted for about 100 patients, in order to match tumours in the CIA data with tumours in the CAS data. From this initial merge, it became evident that there would be difficulties in merging data without a tumour-specific identifier in CIA data. In advance of the merge, a strategy was developed using cancer sites and dates of treatment diagnosis. The strategy was easiest to develop using a small set of patients.

Conducting pilots also worked with merges for each type of new dataset linked to the main dataset. For example, such a pilot facilitated developing a strategy of working with treatment data

that contained many lines of information per tumour. It became evident that these data needed to be handled separately first before merging onto the main dataset.

7.2 Using data in a mature system is most efficient

It is difficult to start a project using data that is in a state of flux. Had this project started when PHE was better-established (e.g. in 2016), there would have been substantially less data work. For the purposes of the DPhil, such a delay was not an option, but it is a lesson for the future.

7.3 Periodically have others check your work

While it may seem inefficient, it is good to pause regularly to double-check that the methods one is applying to collate, clean, and analyse data are in fact what others would also do, as they may have better ideas. Regular communication with PHE colleagues was helpful, as they provided additional strategies and imparted useful insights on how to work with cancer data.

7.4 Structured computer programmes and log files are indispensable

It was very helpful to have set up and maintained a programme structure from the beginning that worked well and that permitted easily understanding what had been done, years later. Each programme developed had the same structure, indicating the purpose of the programme, date of creation, and author, followed by a list of all macros used in the file. All log files and datasets outputted from each programme were saved at the end of a given day, meaning that as programmes were changed over time, a record of former versions was kept. It was possible to go back to older versions to check when certain variables were introduced or when the sample size changed. It was possible to rectify errors by going to back to old versions of files and understanding where and when changes had been made.

7.5 Keep up-to-date written documentation

A Word file was also developed that summarised in bullet points the inputs, outputs, and purposes of each programme, as well as the order in which they were run (Appendix 3, Supplementary Text 5). This document was written such that any programmer would be able to understand what had been done. It would have been best had this file been started at the beginning of the DPhil, rather than half-way through.

Monthly data reports were produced that were shared with collaborators at PHE and DPhil supervisors. These were helpful to obtain comments from collaborators as the project progressed, and they were a useful source of information on decisions made and methods used when reviewing the project later on.

7.6 Balancing meticulousness with efficiency is difficult

Spending time on detail is time-consuming and can result in inefficiency, especially when a problem pertains only to a handful of data points and the dataset is large. However, statistical power was known to be a potential problem in this project, so it was a priority to retain as many patients as possible. It was also known that diagnoses of second cancers could be a source of bias, if patients were not censored at these events (results could be due to the second cancer, not the first). The overall time to manage data might have been reduced by three to five months had records not been checked one by one for patients whose eligibility was uncertain or who had potential second cancers. However, this meticulousness made it possible to identify 1,704 second cancers for a total population of 19,654 (Figure 4.2). Without this effort, analyses of second cancers in lung cancer patients or first invasive cancers in DCIS patients would not have been possible.

8 References

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Chapter 4

Cohort study of patients irradiated with curative intent and recorded in the Oxford Cancer Registry with non-small cell lung cancer, breast cancer, and other sites

1 Background

Chapter 3 describes the development of a study using patient data available through Public Health England (PHE). The Clinical Information Analysis (CIA) dataset was found to contain the necessary information on radiotherapy fractions to conduct an observational study of radiotherapy dose fractionation. In addition, it was determined that data on outcomes and important potential confounders could be obtained through datasets held by Public Health England and directly from hospitals. Having obtained these data, it was necessary to decide which cancer sites to include in such a study.

1.1 Which cancer sites to study?

Cancer sites that might have been suitable for studying associations between radiotherapy fractionation and long-term outcomes and that were available for analysis in the CIA dataset were lung, breast, prostate, head and neck, brain, oesophagus, stomach, prostate, anus, vagina, uterus, cervix, bladder, Hodgkin lymphoma, and non-follicular lymphoma.

A dataset of all eligible patients within the CIA data with these cancer sites was compiled. The largest patient groups in the dataset were breast (N=10,929), prostate (N=3,452), rectal (N=1,192), and head and neck cancers (N=1,188). Among the patients with breast cancer, 10,440 had invasive breast cancer (BC) and 489 ductal carcinoma in situ (DCIS). Radiotherapy for DCIS involves the same dose and fractionation techniques as for invasive BC, so it was decided to study invasive BC and DCIS. Comparing long-term survival after different radiotherapy fractionations in prostate cancer would not have been appropriate, as prostate cancer radiotherapy does not usually aim to improve survival. For rectal cancers, distinguishing between palliative and curative treatment would have been difficult, as five high-dose curative fractions cannot be distinguished from five low-dose palliative fractions without knowing the dose per fraction, and radiation dose

was missing for the vast majority of patients. Head and neck was a group combining 18 sub-sites, for which treatment can differ.

Cancer sites with fewer numbers of patients were considered more difficult to study, due to the possible lack of statistical power. However, the meta-analysis in Chapter 2 suggested that radiotherapy dose has an important effect on survival in non-small cell lung cancer (NSCLC). It was therefore decided also to study NSCLC, though there were only 350 eligible NSCLC patients in this dataset (see page 104). Mortality in NSCLC is high, increasing the number of events, so statistical power might be sufficient even in such a small number of patients. Even if statistical power were a problem, any trends detected might suggest a need for further studies using bigger datasets.

1.2 Lung Cancer

Cancer incidence and mortality in the UK is reported by GLOBOCAN, which provides cancer incidence and mortality by cause for countries world-wide, age-standardised for males and females (1)[1]. Lung cancer was the fourth most-incident cancer for men and women combined at 30.0 per 100,000 people per year, and it was the commonest cause of cancer death in the UK, at 25.4 per 100,000 people per year. NSCLC typically accounts for almost 90% of all lung cancers in developed countries (4).

1.2.1 Treatment of NSCLC in the UK

In the 2006 RCR report, it is estimated that only 15-25% of NSCLC patients are potentially curable (5), though this may be an underestimate and the true proportion may be closer to a third of patients (Geoff Higgins, personal communication). The main curative treatment is surgery, but surgery is only feasible if the cancer is completely resectable and the patient can tolerate it (6). It is not known what proportion of potentially curable NSCLC patients are operable. This is a matter

[1] The population used for standardisation was the World Standard Population proposed by Segi in 1960 (2) and amended by Doll in 1966 (3). This population is very different to an average European population, in that there are many more young people and many fewer old people in this population than in Europe. However, such standardisation permits comparison between countries.

of current research, but a rough guess is that just over half are operable (Geoff Higgins, personal communication). For patients who present with inoperable NSCLC, curative-intent radiotherapy is the main treatment. Patients who are sufficiently fit receive chemotherapy given at the same time as radiotherapy (concurrent chemotherapy), while less fit patients receive chemotherapy before or after radiotherapy (sequential chemotherapy). Patients who are judged not to be fit enough for chemotherapy, including most NSCLC patients, receive radiotherapy only. Conventional radiotherapy dose fractionation has been established as 60 Gy in 30 fractions (7-9). However, the Royal College of Radiologists (RCR) 2006 report *Radiotherapy Dose-Fractionation* (5) listed two other common curative-intent NSCLC regimens: accelerated hypo-fractionated radiotherapy of 52.5-55 Gy in 20 daily fractions (no treatment at weekends) and continuous hyper-fractionated accelerated radiotherapy (CHART) of 54 Gy in 36 fractions, delivered 3 times daily over 12 elapsed days (5). The two fractionations recommended in this report were CHART or conventional radiotherapy (60 Gy in 30 fractions). Interestingly, in the more recent RCR report (December 2016), the 55 Gy in 20 fractionation was listed as a treatment of choice, particularly for patients also receiving either concurrent or sequential chemotherapy (10). This is because of the publication in 2014 of a trial in which patients were given 55 Gy in 20 fractions, randomising patients to concurrent or sequential chemotherapy, which found both groups to have good outcomes (11). There is as yet no trial comparing the 55 Gy in 20 fractionation to conventional or CHART regimens.

1.3 Findings from clinical trials in NSCLC

The meta-analysis in Chapter 2 combined data from all trials that randomised patients with locally advanced NSCLC to different curative-intent dose fractionation regimens. Results of the meta-analysis showed that the benefit of increasing radiotherapy dose differed depending on whether or not concurrent radiotherapy was given. When radiotherapy was given alone, there was a benefit of higher versus lower dose within-trial (median survival ratio, higher versus lower dose,

1.13, 95% CI 1.04-1.22). When concurrent chemotherapy was also given, there was a reduction in median survival for higher compared to lower dose within-trial (median survival ratio, higher versus lower dose, 0.83, 95% CI 0.71-0.97). However, dose escalation is still a subject of interest for NSCLC, even with concurrent radiotherapy, given advances in the reduction of radiation toxicity and an ongoing search for the optimal concurrent chemotherapy regimen (10, 12, 13). The alpha-beta ratio for NSCLC is not well-established, and therefore it is not known whether hyper- or hypo-fractionation may be beneficial (14)[2].

1.4 Breast Cancer

Breast cancer is the commonest incident cancer among women in the UK, at 95.0 per 100,000 women per year, age-standardised, and it was the second commonest cause of cancer death among women in the UK, at 17.1 per 100,000 women per year, age-standardised (1).

1.4.1 Treatment of breast cancer in the UK

For invasive BC and DCIS, the primary curative treatment is surgery, either breast-conserving surgery (BCS) or mastectomy. The decision to treat patients with one or the other is complex, as it is driven by a number of factors: patient choice, tumour size and location, breast size, and tumour-related factors such as family history of breast cancer. For patients with large tumours relative to breast size, mastectomy is recommended (15). This is reflected in the rates of mastectomy among screen-detected patients with invasive BC in the UK in 2008 and 2009 (16). 17% of women with small tumours (<15mm) received mastectomy, compared to 93% with large tumours (>50mm). In addition, 21% with node-negative disease received mastectomy versus 44% with node-positive disease. Thus, on average, women undergoing mastectomy have a poorer prognosis than patients receiving breast-conserving surgery.

[2] See Chapter 1 for an explanation of the terms alpha-beta ratio, hyperfractionation, and hypofractionation.

Chemotherapy is recommended for most invasive BC patients with node-positive cancer. Radiotherapy is recommended as adjuvant treatment for most invasive BC patients who have undergone BCS, due to the possibility of remaining microscopic disease, and for some patients with DCIS after BCS. Radiotherapy is also recommended for some patients with node-positive disease following mastectomy (15, 17). The 2006 Radiotherapy Dose-Fractionation report (5) gave recommendations based on data prior to the publication of the influential UK Standardisation of Breast Radiotherapy (START) trials (18). At that time, while most countries used 50 Gy in 25 fractions, a wide range of radiotherapy fractionations was in use in the UK: 50 Gy in 25 (conventional fractionation), 40 Gy in 15 or 16, 45 Gy in 20, 39 Gy in 13, and 42.9 Gy in 13 fractions. Recommended fractionations in the 2006 RCR Report were 50 Gy in 25, 40 Gy in 15, and 42.5 Gy in 16 fractions. Breast boost dose fractionation practices were varied (details not given), and no specific fractionations were recommended (5). Data from the START trials were first published in 2008, and changes in recommendations following these trials were reflected in the 2016 RCR Report. In this later report, the only recommended fractionation for whole breast/chest wall radiotherapy was 40 Gy in 15 fractions. Breast boosts were recommended for patients with higher-grade invasive cancer, however no specific boost fractionation was recommended. Boosts of 16 Gy in 8 and 10 Gy in 5 fractions were most frequently used in the UK (10). Recommendations for radiotherapy for DCIS were the same as for invasive BC.

1.4.2 Findings from clinical trials in breast cancer

Ten trials comparing radiotherapy fractionations for early-stage invasive BC were identified (Table 4.1) (18-27), using the Early Breast Cancer Trialists Collaborative Group (EBCTCG) search criteria (28). These trials randomised women to different dose-fractionations. Hypofractionation is indicated in the treatment of cancers with low alpha-beta ratios (<10 Gy) to protect normal surrounding tissues[3]. As the alpha-beta ratio for breast cancer is approximately 4 Gy,

[3] See Chapter 1 for an explanation of hypofractionation and the alpha-beta ratio.

Table 4.1: Descriptive summary of breast cancer trials that randomise patients to different radiotherapy dose-fractionations

First author, year (reference)	Years of randomisation	Country	No. patients	Total dose (Gy), no. fractions in trial arms	EQD2T* in trial arms (Gy)	Outcomes measured	Fractionations and outcomes comparable to this study?
Bates, 1988 (19)	1968-1974	UK	411	A: 45-51 in 12 B: 31-35 in 6	A: 55.3-67.3 B: 47.4-57.4	Local recurrence, metastases, overall survival, acute and late side effects	No
Dvivedi, 1978 (22)	1975-1976	India	25	A: 45 in 23 B: 33.5 in 5	A: 41.1 B: 56.5	No numeric estimates reported	No
Baillet, 1990 (21)	1982-1984	France	230	A: 23 in 4 B: 45 in 25	A: 34.0 B: 38.7	Overall survival, local-regional recurrence, late side effects	No
Spooner, 2012 (23)	1985-1992	UK	707	A: 50 in 25 B: 40 in 15	A: 44.6 B: 44.6	Locoregional recurrence, overall survival, recurrence-free survival	No
Haviland, 2013 (18) (START A)	1998-2001	UK	2236	A: 50 in 25 B: 41.6 in 13 C: 39 in 13	A: 44.6 B: 45.4 C: 41.2	At 10 years: local recurrence, local-regional recurrence, distant recurrence, any breast-cancer related event, all-cause mortality, number of deaths due to breast cancer, acute and late side effects	Yes
Haviland, 2013 (18) (START B)	1999-2001	UK	2215	A: 50 in 25 B: 40 in 15	A: 44.6 B: 44.6	At 10 years: local recurrence, local-regional recurrence, distant recurrence, any breast-cancer related event, all-cause mortality, number of deaths due to breast cancer, acute and late side effects	Yes
Goel, 2000 (26)	1989-1992	India	104	A: 45 in 20 B: 40 in 17	A: 43.9 B: 41.6	Local recurrence, metastasis, side effects †	No
Whelan, 2002 (24)	1993-1996	Canada	1234	A: 50 in 25 B: 42.5 in 16	A: 44.6 B: 46.8	Local recurrence, distant recurrence, recurrence-free survival, disease-free and overall survival, cosmesis, acute and late side effects	No
Barsoum, 2010 (25)	Not reported	Egypt	308	A: 50 in 25 B: 40 in 15	A: 44.6 B: 44.6	Overall survival, disease-free survival (local and distant), early and late side effects, cosmesis †	No
Agrawal, 2011 (20) (FAST)	2004-2007	UK	915	A: 50 in 25 B: 30 in 5 C: 28.5 in 5	A: 44.6 B: 46.8 C: 42.9	Cosmesis, radiation-induced changes, local recurrence, disease-free survival	No
Brunt, 2016 (27) (FAST-Forward, toxicity sub-study)	2011-2012	UK	352	A: 40 in 15 B: 27 in 5 C: 26 in 5	A: 44.6 B: 48.1 C: 45.6	Acute skin toxicity	No

* EQD2T is calculated in terms of 2 Gy biologically effecive dose per fraction, corrected for total treatment time. Trials are presented in order of the first year of randomisation.

† Proportions only reported, not hazards.

Abbreviations: EQD2T=equivalent dose in 2 Gy fractions, corrected for time. START=STAndardisation of UK RadioTherapy. FAST=Faster radiotherapy for breast cancer patients.

experimental arms were hypofractionated in all of these trials (18, 24, 29). Seven trials reported overall survival, though only three of these reported hazard ratios. Two trials reported the number of deaths caused by breast cancer. Three trials reported disease-free survival. Eight trials reported breast cancer recurrence. Two trials reported a hazard of developing any breast-cancer related event (including breast cancer survival) (18). One publication was of a sub-study reporting preliminary results of a trial for which full results are not yet available; this publication reported only on acute skin toxicity (27). Some trials were conducted in resource-poor settings, in which the aim was to reduce the number of radiotherapy fractions to minimise the burden on the treatment system; in these settings patient follow-up was especially difficult (22).

In more recent trials of hypo-fractionation in the UK and Canada, the aim was to establish equivalence of hypo-fractionated regimens with the conventional one. These trials found that the hypo-fractionated regimens (40 Gy in 15, 41.6 Gy in 13, 39 Gy in 13, and 42.5 Gy in 16 fractions) were equivalent to 50 Gy in 25 fractions in terms of loco-regional recurrence and in terms of survival, where measured (18, 24). None of the trials identified aimed to increase the biologically effective radiotherapy dose. This makes it difficult to use the randomised trials to assess the effect of increasing radiotherapy dose.

1.5 Aims of the study

The variability in UK radiotherapy practice that existed in the early and mid-2000s is an opportunity to study the effects such variability might have had on long-term outcomes in invasive BC, NSCLC, and DCIS. However, it is unclear whether insight into the effects of different radiotherapy fractionations can be gained using observational data. In this context, a cohort study was conducted of all patients in the Oxford CIA data who received curative-intent radiotherapy for the treatment of inoperable NSCLC, invasive BC, and DCIS. The following questions were addressed for each of the cancer sites studied:

NSCLC:

1. Is intended, time-corrected radiotherapy dose[4] associated with lung-specific survival?
2. Is there any association of intended, time-corrected radiotherapy dose with overall survival and with the risk of developing a non-lung-cancer-related second primary cancer?

Invasive BC:

1. Is intended, time-corrected radiotherapy dose associated with the risk of developing any breast-cancer related event (recurrence, metastases, contralateral breast cancer, or breast cancer death)?
2. Is there any association of intended, time-corrected radiotherapy dose with breast cancer-specific survival, overall survival, or non-breast-cancer survival?

DCIS:

Is intended, time-corrected radiotherapy dose associated with developing invasive BC?

The results were compared with published data from randomised trials.

For completeness, methods are described for the compilation of a dataset including patients with all potentially eligible cancer sites, not just NSCLC and breast. In addition, numbers of patients in each cancer site are tabulated by the number of radiotherapy fractions recorded.

[4] In order to compare different radiotherapy fractionations, total dose was converted to equivalent dose in 2 Gy fractions, corrected for overall treatment time.

2 Methods

2.1 Data sources used in this study

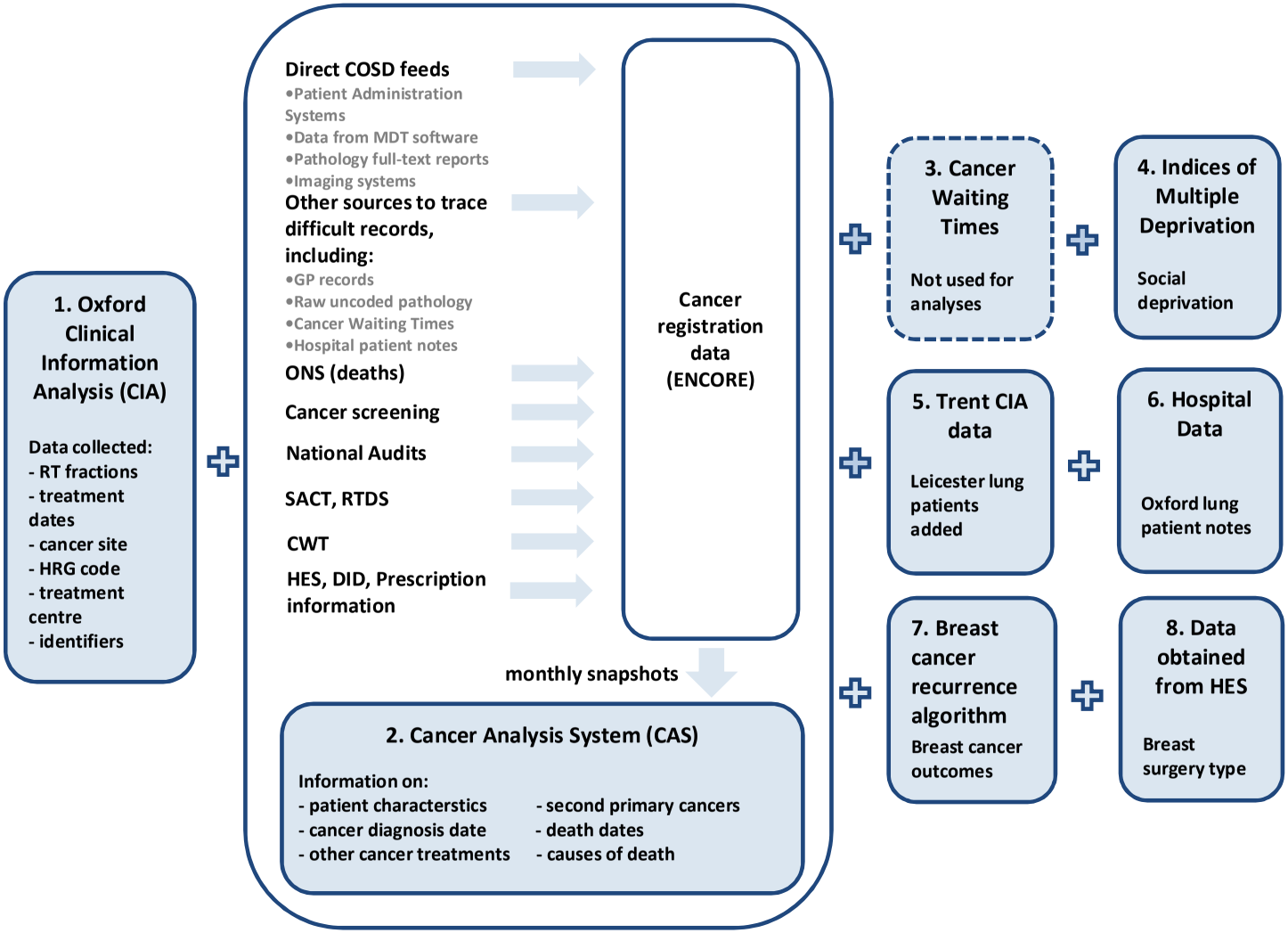
Multiple data sources were brought together in this study to obtain the necessary variables to conduct an analysis of radiotherapy fractionation and outcomes in cancer patients. It was necessary to have information not only on radiotherapy and outcomes, but also on potential confounders and effect modifiers. The data sources identified for this study are described below and depicted pictorially in Figure 4.1.

2.1.1 Cancer Information Analysis (CIA) dataset

Between the years 1999 and 2011, the Oxford Cancer Intelligence Unit (OCIU) collected data on number of radiotherapy fractions (available for 87% of patients), treatment start and end dates, cancer site, healthcare resource group code (a financial coding system used within the NHS to allocate payment for treatments), forename and surname, NHS identification number (2004 onwards), birthdate, post code, treatment centre, and treatment provider. There were also other pieces of information collected that were missing for the vast majority of patients and thus not useable for this study, including radiation dose, anatomical region irradiated, tumour size, and intent of radiotherapy. Identifiable data were collected only from 2004 onwards, so the study was restricted to the years 2004 to 2011.

2.1.2 Cancer Analysis System

The Cancer Analysis System (CAS) is the data source used within PHE for analytical purposes. All information in CAS comes from multiple data sources that feed into the English National Cancer Online Registration Environment (ENCORE), where data are managed on an ongoing basis. ENCORE data undergo constant change, but once per month a version is saved as the “snapshot” from that month, which forms CAS.



Abbreviations: HRG= healthcare resource group; COSD = Cancer Outcomes Services Dataset; MDT = multi-disciplinary team; ONS = office of national statistics; GP = general practice; ENCORE = English Online Registration Environment; SACT = systemic anti-cancer therapy; RTDS = radiotherapy dataset; CWT = cancer waiting times; HES = hospital epidodes statistics; DID = diagnostic imagine dataset.

Figure 4.1: Data sources for the cohort study. This figure shows the order in which data sources were brought together (left to right) and the order in which information feeds into the Cancer Analysis System at Public Health England (top to bottom).

The core of cancer registration data is the Cancer Outcomes and Services Dataset (COSD, data feeds from hospitals), as well as a few additional sources consulted to obtain information on records difficult to trace (Figure 4.1). To these core data are added vital statistics from the Office of National Statistics (ONS), cancer screening data, information from national audit reports, Systemic AntiCancer Treatment (SACT) data, the RadioTherapy DataSet (RTDS), Cancer Waiting Times (CWT), Hospital Episodes Statistics (HES), the Diagnostic Imaging Dataset (DID), and prescription information. Figure 1 in Appendix 3 is the official depiction of data held at PHE and includes further detail.

2.1.3 Cancer Waiting Times

Cancer Waiting Times is a dataset which contains information on whether a cancer diagnosis is for a primary cancer, recurrence, or metastasis. Data are available only from 2009 onwards. Initially, it was planned to use these data to obtain recurrence information. However, the later availability of a breast cancer recurrence algorithm was preferred to using just Cancer Waiting Times for analyses. This was because the recurrence algorithm included data from Cancer Waiting Times but also several other sources (especially Hospital Episodes Statistics), and recurrence information was available for the whole study period. Initial merges with Cancer Waiting Times allowed some patients ineligible for the study to be identified.

2.1.4 Indices of Multiple Deprivation

The Department for Communities and Local Government periodically publishes indices of multiple deprivation (IMD) for use as a measure of social deprivation at the local area level (lower super output area, a UK census zoning unit) (30). These data are publicly available.

2.1.5 Trent CIA data

The Trent Cancer Registry also collected radiotherapy data between 2004 and 2011, but these data were not possible to use on a large scale as they were not stored in a similar manner. However, it was possible to obtain ten additional NSCLC patients from this dataset.

2.1.6 Hospital data

Our study protocol detailed plans to obtain additional data directly from centres where patients were treated to receive information on some of the late side-effects of radiotherapy and on prostate specific antigen levels for prostate cancer patients. However, it was not possible to pursue the hospital data for this study on a systematic scale, as different hospitals use different identifiers and these cannot all be linked to NHS numbers (Chapter 3). It was possible, however, to use hospital data to conduct a small sub-study of NSCLC patients treated at Oxford University Hospitals.

2.1.7 Breast cancer recurrence algorithm

Using data available within CAS as well as other direct sources of data within the NHS (especially HES), an effort is underway by Oxford University and PHE colleagues to reliably identify cancer recurrence in invasive BC patients, known hereafter as “the recurrence algorithm” (Gurdeep Mannu, personal communication). The algorithm was used to obtain information for invasive BC patients in this study on recurrences, metastases, contralateral breast cancers, and breast cancer death.

2.1.8 Data directly obtained from hospital episodes statistics (HES)

Though CAS does contain information on treatment, these data were not complete and completeness varied by treatment centre. It was possible, however, to obtain data on breast surgery type directly from HES, much improving the completeness of this variable.

2.2 Producing a dataset including eligible patients for all available cancer sites

Before producing a dataset just including NSCLC, invasive BC, and DCIS patients, data were collated for all cancer sites for which patients received radiotherapy of curative intent. Patients were selected for inclusion in the dataset, according to a set of inclusion and exclusion criteria. Data were collated from a number of different sources.

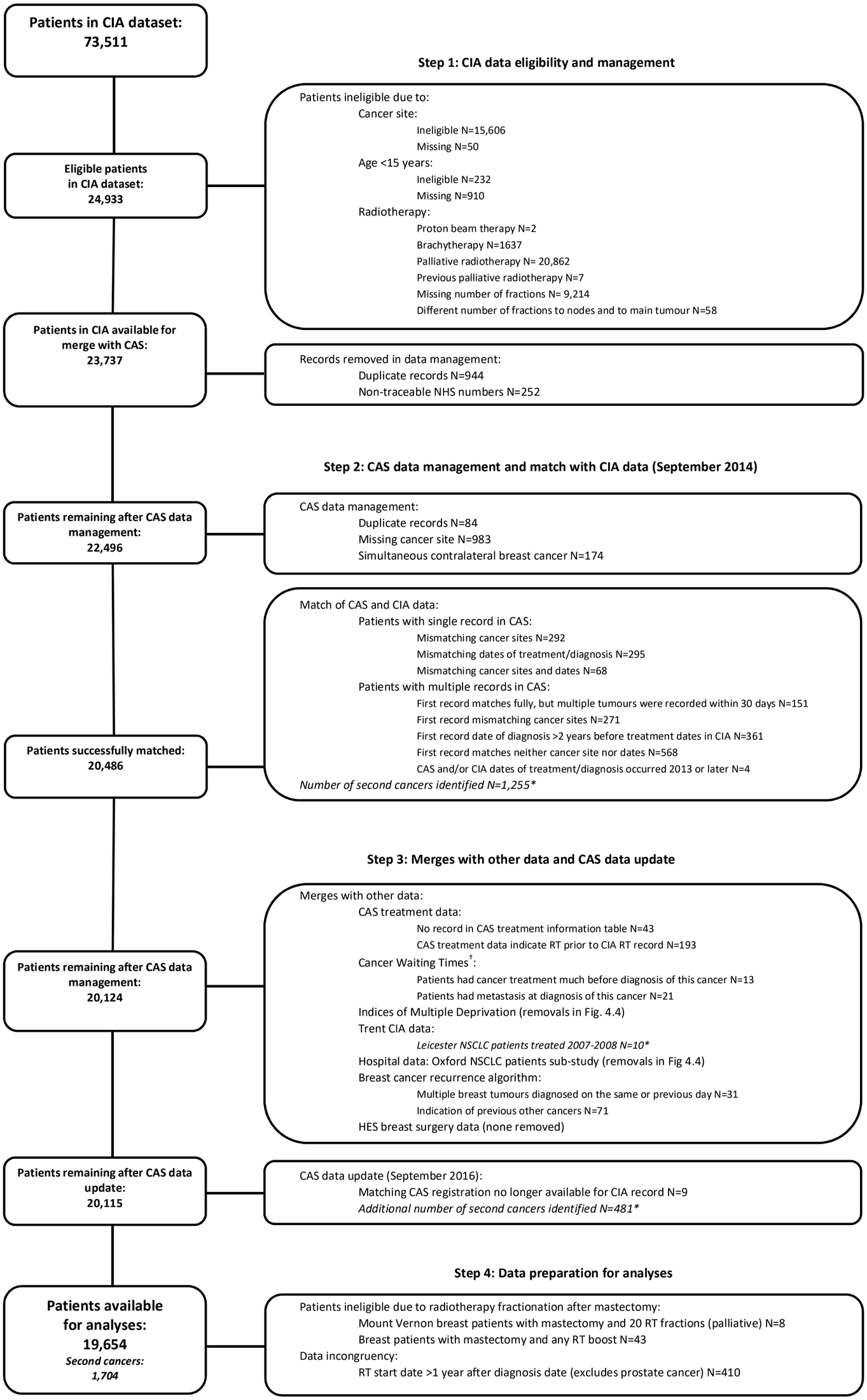
2.2.1 Inclusion and exclusion criteria

Patients were included in a final dataset who lived in the OCIU catchment area and were treated with external beam radiotherapy of curative intent for either DCIS or an invasive cancer of one of the following sites: NSCLC, breast, bladder, brain/central nervous system, head and neck, prostate, rectum, Hodgkin lymphoma, non-follicular lymphoma, or gynaecological cancers. Their tumour must have been the first record of invasive cancer other than non-melanoma skin cancer. Patients needed to be aged 15 or above at the time of treatment. Treatment intent was derived for each cancer site based on number of radiotherapy fractions and healthcare resource group codes, according to guidelines developed by CIA dataset managers at PHE and the 2006 Royal College report (5). Patients with bilateral cancers were excluded.

2.2.2 Data collation and management

Including patients diagnosed with any of the above eligible cancer sites, a series of data management and merging steps were undertaken to produce a dataset for analyses. The order in which data sources were added is shown in Figure 4.1. The steps taken to manage and merge data are shown in Figure 4.2.

The core dataset for this study was the CIA. As a first step, eligible patients were identified and data records cleaned. The CIA data were then merged with CAS (step 2). In CAS, each individual's



* These records were added to the dataset, not removed

Abbreviations: RT=radiotherapy, CAS=Cancer Analysis System, CIA=Clinical Information Analysis, NHS=National Health Service, PHE=Public Health England.

† Cancer Waiting Times data were not used for analyses, but ineligible patients were identified in a prelinary merge.

Figure 4.2: Steps taken to manage and merge datasets. Record exclusions and additions are shown in the order in which they occurred. Records are removed unless otherwise stated.

tumour has its own identifier. However, the CIA data do not have tumour-specific identifiers, only person-specific NHS numbers. Individual tumour records in CAS had to be matched to tumours in CIA using NHS number (CIA and CAS), information on cancer site (CIA and CAS), diagnosis date (CAS), and dates of radiotherapy treatment (CIA). CIA and CAS records were considered to be matches if cancer sites were the same and dates of treatment occurred up to a year before diagnosis and up to two years after diagnosis (allowing for data inconsistency). For cancers sites that did not match, these were manually sorted to determine whether they could still be matches (for instance a diagnosis of "rectosigmoid junction" in CAS and "rectum" in CIA are likely to describe the same cancer). For patients with multiple cancer sites in CAS, the first recorded cancer had to match the CIA data or the patient was excluded. If the first record matched CIA, then subsequent records were either determined to be duplicates in CAS, recurrences of the first primary cancer, or second primary cancers.

A third step was to merge the core CIA and CAS data to other available data sources and to update the original merge with CAS to obtain the newest data. While treatment data are also contained within the CAS system, there can be many treatments for the same tumour. Treatment data were managed as a separate dataset and "reshaped" so that these multiple records per person could be merged as a single line of data onto the main CIA-CAS dataset. Cancer Waiting Times data were obtained from the West Midlands PHE office, with the aim of extracting information on recurrence (this effort was cut short when the recurrence algorithm became available). To obtain a measure of social deprivation, IMD data were obtained and merged onto the main dataset. It was possible to extract data from the Trent CIA for NSCLC patients who were treated at Leicester after the years for which data were available in the Oxford CIA data. Ten more patients could be added to the dataset treated in 2007 and 2008.

Ethical permissions obtained for the study protocol covered the use of data directly obtained from hospitals. It was therefore possible to obtain all available notes for NSCLC patients treated in

Oxford (details on page 96). Patients were identified using NHS number, hospital number (where available), names, and dates of birth.

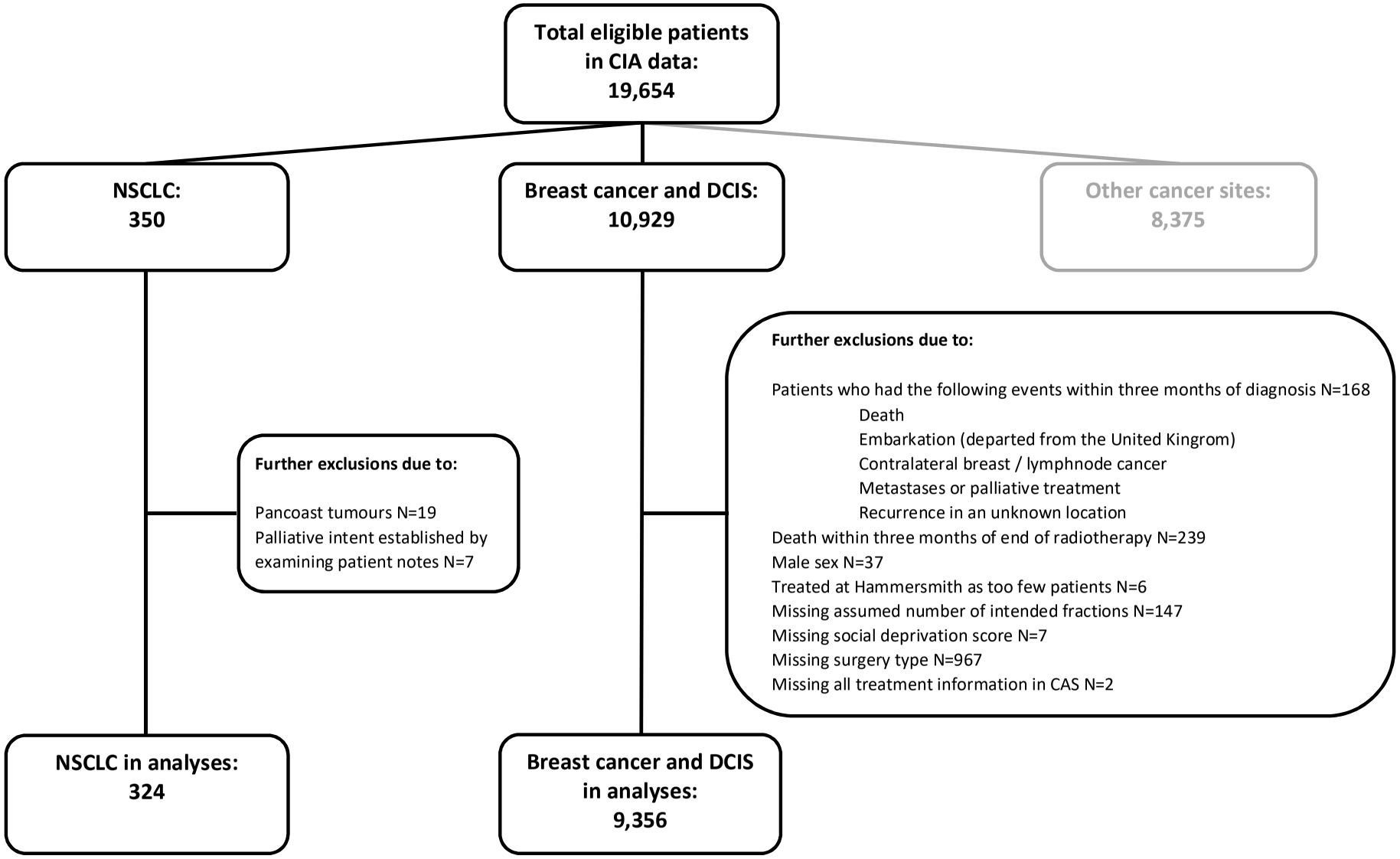
The breast cancer recurrence algorithm became available to use for this study in February 2017. The algorithm was run including all tumour identifiers for eligible women with invasive BC in this study and information on the first event identified was merged onto the main dataset. Finally, it was possible to obtain breast surgery information directly from HES to supplement missing information in CAS treatment data.

CAS data are updated each month. As the initial CAS merge with CIA had occurred in September 2014, this was repeated in September 2016, prior to preparing data for analyses. Corrections to primary cancer records and additional second primary cancers were incorporated into the main data.

The final step was then to create variables and smaller datasets suitable for analysis. Any outstanding data inconsistencies were also addressed.

2.3 Producing a dataset including NSCLC, invasive BC, and DCIS patients

After a final dataset for analysis was obtained, the decision was made to study NSCLC and breast cancer. Additional exclusions were made specific to these cancer sites (Figure 4.3). NSCLC patients were excluded who had Pancoast tumours or whose notes revealed they had been treated with palliative intent. Breast cancer patients were excluded if they died, embarked (departed from the United Kingdom), or had breast cancer events within three months of diagnosis, if they died within three months of end of radiotherapy, were male, were treated at Hammersmith (N=6), or they were missing information on intended fractions, social deprivation, type of surgery, or all CAS treatment information.



Abbreviations: NSCLC=non-small cell lung cancer. CIA=Clinical Information Analysis. DCIS=ductal carcinoma in situ. CAS=Cancer Analysis System

Figure 4.3: Number of patients further excluded from analyses for site-specific reasons

2.4 Variables used in analyses: source datasets and coding

All variables used and their source datasets are listed (Table 4.2 and Appendix 3, Supplementary Text 1, for details). Information on patient characteristics, including age at diagnosis, sex, social deprivation, history of serious comorbidity, and smoking status, came from CAS, the Indices of Multiple Deprivation (30), and hospital data. Tumour information, including cancer site, stage, number of nodes involved, morphology, and laterality came from CAS with the addition of stage data for Oxford NSCLC patients from hospital data.

All information on radiotherapy treatment was obtained from the CIA dataset, to include treatment centre, number of fractions, and dates of treatment. EQD2T was calculated using an alpha-beta ratio of 10 for NSCLC and an alpha-beta ratio of 4 for invasive BC and DCIS (14, 18, 24, 29, 31). Two types of EQD2T were calculated: "intended" and "actual." For intended EQD2T, assumptions were made about the intended number of fractions for patients who had a record of a non-standard number of fractions. Standard numbers of fractions for NSCLC were 20, 25 (Pancoast tumours – excluded), 30, 32, 33, and 36 (Table 4.3). Standard numbers of fractions for breast cancer were 12, 13, 15, 16, 18, 20, 23, 25, 28, and 30 (Table 4.4; further details in Appendix 3, Supplementary Text 3). If a patient had a non-standard number of fractions, the next-higher number of standard fractions was assumed to be intended for that patient. For example, a breast cancer patient who had a record of 29 fractions was assumed to be intended to have 30 fractions. For intended EQD2T, an average intended treatment time was calculated based on the intended number of fractions (as in Chapter 2). For actual EQD2T, treatment start and end dates in patients' records were used to obtain treatment time. Analyses using actual EQD2T excluded any patients whose recorded information on number of fractions and on treatment time was implausible, as these were likely to be recording errors.

Intended EQD2T was considered to be the preferred type of EQD2T to study. This is because intended EQD2T reflects what oncologists judged to be appropriate for their patients at the start

Table 4.2: List of variables used for analyses in PHE study

1. Patient information

Variable	Source dataset	Patients for whom variable is used in analyses
Age at diagnosis	CAS	All
Sex	CAS	All
Level of social deprivation (IMD quintiles)	Indices of Multiple Deprivation	All
History of any serious comorbidity	Hospital Data	Oxford NSCLC
Smoking status at diagnosis	Hospital Data	Oxford NSCLC

2. Tumour information

Variable	Source dataset	Patients for whom variable is used in analyses
Cancer site	CAS	All
Diagnosis date	CAS	All
Cancer stage	CAS (breast), Hospital Data (NSCLC)	Breast, Oxford NSCLC
Number of nodes involved	CAS	Breast
Morphology	CAS	All
Laterality	CAS	All

3. Treatment information

Variable	Source dataset	Patients for whom variable is used in analyses
Treatment centre	CIA	All
Treatment year	CIA	All
Number of radiotherapy fractions	CIA	All
Intended radiotherapy treatment time	CIA	All
Actual radiotherapy treatment time	CIA	All patients with standard RT start and end date information
Intended EQD2T	Derived based on CIA	NSCLC
Actual EQD2T	Derived based on CIA	Eligible NSCLC
Intended EQD2T to whole breast	Derived based on CIA	Breast, DCIS
Intended EQD2T to tumour bed (including boost dose)	Derived based on CIA	Eligible Breast, DCIS
Actual EQD2T to tumour bed (including boost dose)	Derived based on CIA	Eligible Breast, DCIS
Any surgery of curative intent	CAS	All
BCS or mastectomy	HES and CAS	Breast, DCIS
Any cytotoxic chemotherapy	CAS	All
Whether chemotherapy sequential or concurrent to radiotherapy	Hospital Data	Oxford NSCLC
Hormone therapy	CAS	Breast, DCIS
HER-2 treatment	CAS	Breast, DCIS

Table continued on next page.

Table 4.2 continued: List of variables used for analyses in PHE study

4. Outcome information

Variable	Source dataset	Patients for whom variable is used in analyses
Cancer-specific death yes/no	CAS	NSCLC, breast
Death not due to breast cancer yes/no	CAS	Breast
Death due to any cause yes/no	CAS	NSCLC, breast
Date of death	CAS	All
Second cancer yes/no	CAS	NSCLC, breast
Second cancer site	CAS	NSCLC, breast patients who had second cancer
Subsequent invasive breast cancer yes/no	CAS	DCIS
Date of second/invasive cancer diagnosis	CAS	All patients who had second cancer
Breast cancer recurrence (local, distant) yes/no	Breast cancer recurrence algorithm	Breast
Date of breast cancer recurrence	Breast cancer recurrence algorithm	Breast patients who had recurrence

Table 4.3: NSCLC: Assumed radiotherapy fractionations based on number of fractions indicated in CIA dataset*.

	Oxford			Reading			Northampton			Leicester		
No. fractions	**No. patients**	**Total dose (Gy)**	**Intended EQD2T (Gy)**	**No. patients**	**Total dose (Gy)**	**Intended EQD2T (Gy)**	**No. patients**	**Total dose (Gy)**	**Intended EQD2T (Gy)**	**No. patients**	**Total dose (Gy)**	**Intended EQD2T (Gy)**
16	1	*55*†										
17				2	*55*†							
18				1	*55*†							
19				3	*55*†							
20	71	55 (50)‡	55.1 (48.8)‡	48	55	55.1	38	55	55.1	18	55	55.1
23	1	*54*§¦										
26				1	*60*¶		1	*60*¶				
27	1	*54*§¦		1	*60*¶							
28							1	*60*¶				
30				9	60	49.7	15	60	49.7			
32	1	64	52.3	1	64	52.3	17	64	52.3			
33	2	66	53.6				3	66	53.6	4	66	53.6
35										1	*54*§¦	
36	71	54¦	51.8							12	54¦	51.8
Total non-standard	3/148			8/66			2/75			1/35		

* Fractions assumed to be given daily minus weekends, unless otherwise stated. Blue numbers in italics are the assumed total dose patients were intended to receive. These patients received non-standard numbers of fractions.

† 20 intended fractions assumed.

‡ Review of patient notes showed 10 patients had received 50 rather than 55Gy total dose. The EQD2T for these patients was calculated to be 48.8Gy rather than 55.1Gy.

§ 36 intended fractions assumed.

¦ Fractions delivered three per day, with no break over the weekend (CHART)

¶ 30 intended fractions assumed.

Abbreviations: NSCLC=Non-Small Cell Lung Cancer. CIA=Clinical Information Analysis. EQD2T=time-corrected dose in 2Gy equivalent fractions. CHART=Continuous Hyperfractionated Accelerated RadioTherapy.

Table 4.4: Breast: Assumed radiotherapy fractionations based on number of fractions indicated in CIA dataset*.

	Oxford			Reading			Northampton			Mount Vernon			Leicester		
No. fractions	**No. patients**	**Fractionation**	**Intended EQD2T (Gy)†**	**No. patients**	**Fractionation**	**Intended EQD2T (Gy)†**	**No. patients**	**Fractionation**	**Intended EQD2T (Gy)†**	**No. patients**	**Fractionation**	**Intended EQD2T (Gy)†**	**No. patients**	**Fractionation**	**Intended EQD2T (Gy)†**
11	1	*41.6 in 13‡*		4	*40 in 12§*		2	*40 in 15*							
12				190	40 in 12§	46.8									
13	1,246	41.6 in 13‡	45.4	9	*40 in 15*										
14	2	*40 in 15*		1	*40 in 15*		1	*40 in 15*							
15	381	40 in 15 41.6 in 13‡	44.4	77	40 in 15 *40 in 15*	44.4	701	40 in 15 *40 in 15*	44.4	491	40 in 15	44.4	85	40 in 15	44.4
16	742	+7.5 in 3¦ *40 in 15*	45.4 (50.8)	8	*+9 in 3* *40 in 15*		1	*+9 in 3* *40 in 15*			*40 in 15*				
17	3	*+10 in 5* *40 in 15*		13	*+9 in 3* 40 in 15		1	*+9 in 3* 40 in 15		1	*+9 in 3* 40 in 15	44.4			
18	12	*+10 in 5*		368	+9 in 3	44.4 (53.4)	16	+9 in 3 *40 in 15*	44.4 (53.4)	588	+10.5 in 3 *40 in 15*	(56.1, 57.6)			
19				5	*50 in 25*		17	*+10 in 5*		2	*+10 in 5*				
20	182	40 in 15 +10 in 5	44.4 (51.8)	4	*50 in 25*		1,459	45 in 20 *45 in 20*	44.20	81	40 in 15 +10 in 5	44.44 (54.0)	177	45 in 20	43.50
21				1	*50 in 25*		7	*+9 in 3* *45 in 20*							
22				1	*50 in 25*		1	*+9 in 3* 45 in 20							
23				2	*50 in 25*		106	+9 in 3	44.2 (53.1)						
24				7	*50 in 25*		11	*50 in 25*							
25	394	50 in 25	44.6	38	50 in 25 *50 in 25*	44.6	248	50 in 25 *45 in 20*	44.6	38	50 in 25	44.6	533	50 in 25	43.6
26				1	*+10 in 5* *50 in 25*		3	*+16 in 8* *45 in 20*							
27				1	*+10 in 5*		1	*+16 in 8*							
28	6	*50 in 25* *+10 in 5* *50 in 25*		3	*50 in 25* *+10 in 5* *50 in 25*		40	45 in 20 +16 in 8 *50 in 25*	44.2 (57.7)	12	50 in 25 +10.5 in 3	44.6 (57.7)			
29	3	*+10 in 5*		5	*+10 in 5*		2	*+10 in 5*							
30	153	50 in 25 +10 in 5	44.6 (51.8)	339	50 in 25 +10 in 5	44.6 (51.8, 54.6)	41	50 in 25 +10 in 5	44.6 (51.8)	11	50 in 25 +10 in 5	44.6 (51.8)			
Total non-standard	26/3,125			62/1,077			45/2,658			3/1,224			0/795		

* Fractions assumed to be given daily minus weekends, unless otherwise stated. Blue numbers in italics are the assumed total dose (Gy) and number of fractions patients were intended to receive. These patients received non-standard numbers of fractions.
† Whole breast dose (Doses including boost). Doses including boost may differ within centre due to changes in overall treatment time, by calendar year. See Appendix 3, Figure S4 for details.
‡ 5 fractions delivered per fortnight
§ 3 fractions delivered per week
¦ fractions delivered every other day

Abbreviations: CIA=Clinical Information Analysis. EQD2T=time-corrected dose in 2 Gy equivalent fractions.

of treatment. The use of intended EQD2T is analogous to analysing randomised trials according to intention to treat. Actual EQD2T more accurately reflects the dose received by the patient, but what patients actually receive is influenced by a number of factors arising during the treatment course. Results of actual EQD2T analyses could however be conducted to check for differences with results of intended EQD2T analyses.

Other treatment information was obtained from CAS. Information on breast surgery type was supplemented with information directly obtained from HES. The timing of chemotherapy (concurrent or sequential) was determined for Oxford NSCLC patients in hospital data.

All information on death and second primary cancers was obtained from CAS. Type of death outcomes included any death, cancer-specific death, and non-breast-cancer death (invasive breast cancer only). Non-breast-cancer death included any cause of death other than breast cancer. Dates of exit from follow-up for any cause of death were either the date of death or 31 December, 2016, if the patient was still alive.

Second primary cancers (NSCLC only) included any non-lung-cancer primary cancers that occurred at least 30 days after the diagnosis of the initial NSCLC (see Appendix 3, Supplementary Text 1 for details). First invasive breast cancer in DCIS patients included invasive breast cancers that occurred at least 365 days after the initial DCIS diagnosis. Dates of exit from follow-up for any second primary cancer in NSCLC patients, or first primary invasive breast cancer in DCIS patients, were the date of the first event or 30 April, 2016.

Breast recurrence type and date was obtained from the recurrence algorithm. Dates of exit from follow-up for any breast-cancer related event were the earliest date of any event, any non-breast-cancer death, or 31 December, 2016.

2.5 Examination of NSCLC patient notes in Oxford

When planning NSCLC patient multivariable analyses, it became evident that some important confounding variables were not available, especially stage. A pilot study of 20 patients treated in Oxford was conducted, to determine whether and which additional pieces of information could be obtained from patient notes. This pilot study was successful, and information was obtained on stage, smoking status, comorbidity, and details of chemotherapy for all Oxford patients for whom notes could be found. In addition, key CIA and CAS data were checked and supplemented: whether or not radiotherapy and other treatments had taken place, dates of all treatments, tumour laterality, stage as it was available in CAS, and number of radiotherapy fractions (both intended and actual).

Once the data were obtained, these were examined in terms of completeness, the degree to which they differed from data in CIA and CAS, and their impact on results obtained in fractionation analyses. Details of newly collected variables and how they were coded are also available (Appendix 3, Supplementary Text 1).

2.6 Descriptive analyses (NSCLC, invasive BC, and DCIS)

Data were analysed separately by cancer site (NSCLC, invasive BC, DCIS). Descriptive analyses included histograms of radiotherapy fractionations by treatment centre, calendar period, and number of treatment days. Radiotherapy fractionations and all potential co-variates were cross-tabulated in contingency tables and chi squared tests of association conducted by all outcomes of interest. Chi squared tests of association were also conducted between all potential covariates and intended EQD2T.

Chi squared tests were conducted by testing whether the observed values in cells of the contingency tables differed statistically significantly from expected values, according to the following formula (32):

$$\chi^2 = \sum \frac{(O-E)^2}{E}, on\ (r-1)\ \text{x}\ (c-1)\ degrees\ of\ freedom,$$

where *O* is the observed value in a given cell of the contingency table, *E* is the expected value in that same cell, *r* is the total of number rows in the contingency table, and *c* the total number of columns. The expected value of a cell is the column total multiplied by the row total, divided by the overall total in the table. In order to maximise the number of patients, missing values for a variable were given a separate code and still included in the analyses. Therefore, these chi squared tests included also the missing categories of all variables.

In addition, when categories of a tabulated exposure (or independent) variable were ordered (for example age), a chi squared test for linear trend was conducted. This test assesses on one degree of freedom whether the log odds in the exposure group increased across the categories of the variable (32). Chi squared tests for trend conducted in this study excluded patients missing values for these variables.

2.7 Survival analyses (NSCLC and invasive BC)

2.7.1 Statistical methods

Survival analyses were conducted using the method of Kaplan-Meier (33) and by fitting Cox proportional hazards models (34) in the computer package Stata version 13.1 (35).

In Kaplan-Meier plots (33), survival in terms of the main outcome of interest was plotted by categories of intended EQD2T. Heterogeneity in the survivor functions between these categories of intended EQD2T was tested using a log rank test (32). In this test, the null hypothesis is that the survivor functions for different categories of EQD2T are not statistically different from one another. Observed versus expected numbers of events within each category of EQD2T are compared to obtain the test statistic, which is referred to the chi squared distribution on one degree of freedom. The expected number of events is the number of events that would occur

were there no difference between the groups. In addition, a log rank test for linear trend across categories of EQD2T was conducted (36). This test for trend is an extension of the log rank test of heterogeneity, referred to the chi squared distribution on one degree of freedom.

In Cox proportional hazards models (34), several tests of statistical significance were conducted. P-values presented for each level of a categorical exposure variable were produced using Wald tests (32). A Wald test statistic is based on a fitted quadratic approximation to the log likelihood ratio. For continuous exposure variables, Wald tests were also conducted, assessing the presence of a linear trend in the variable.

In addition to tests of significance for individual parameters in models, overall (joint) tests of multiple parameters were also conducted. Such overall tests were conducted to assess the association of a categorical variable as a whole with the outcome, for example categorical intended EQD2T. These were likelihood ratio tests comparing a model including all parameters with a model excluding the parameters of interest (32).

Likelihood ratio tests of this kind, in which one model is a reduced or simpler version of a second more complex model, were conducted using the following formula:

$$Likelihood\ ratio\ test\ statistic = -2 \text{ x } \left(L_{simple\ model} - L_{complex\ model}\right),$$
$$on\ c - s\ degrees\ of\ freedom,$$

in which *L* is the likelihood of a given model, *c* is the number of parameters in the complex model, and *s* is the number of parameters in the simpler model. The likelihood ratio test statistic is referred to the chi squared distribution.

This same method of a likelihood ratio test comparing a more complex model with a simpler model was also used to assess the presence of effect modification (32). In this case, the model with effect modification included more parameters (complex model) and the one without included fewer (simpler model).

2.7.2 Modelling strategy

To produce a final model for each question of interest for NSCLC and breast cancer, a series of unadjusted and adjusted analyses was produced for the main questions of interest to assess which variables to retain in a final model. In these initial models, intended EQD2T was examined as a categorical variable. A Kaplan-Meier plot[5] was produced as well as a univariable Cox proportional hazards model. In a fully adjusted model including all available co-variates for that cancer site in categorical form, adjusted associations between each variable and the main outcome were assessed.

2.7.2.a Confounding

To maximise statistical power, only co-variates considered to be possible confounders were retained in a final model. Confounding was assessed by examining the model including all co-variates (full model) with a model excluding each of the potential confounders, one by one. If the hazard ratios for each of the categories of intended EQD2T remained similar to the full model, the omitted variable was not considered to be a confounder. If hazard ratios in only some categories of intended EQD2T were different and the differences were small, the omitted variable was considered a slight confounder. If hazard ratios were different in most categories or if there was a big change in one or more categories, the omitted variable was considered to be a moderate confounder. If hazard ratios in most categories were very different, the omitted variable was considered to be a major confounder.

Final models for all outcomes for a given cancer site contained the same co-variates, to facilitate comparison of results for different outcomes. The exception to this was non-breast-cancer survival, which had a different set of confounders. For this outcome, one model is shown with the same co-variates as for other outcomes, and a second model is shown adjusting for confounders specific to non-breast-cancer survival.

[5] Kaplan-Meier plots are univariable, as they cannot be adjusted for other factors.

2.7.2.b Categorical or continuous form of EQD2T

Including EQD2T as a categorical variable makes no assumptions about the type of association between dose and the outcome. Including EQD2T as a continuous variable increases statistical power and permits testing for a linear trend in the effect of dose. After confounders were identified, models with EQD2T as continuous and as categorical were compared. A likelihood ratio test was conducted with the hypothesis that the model with more parameters (categorical EQD2T) was not a better fit to the data than the model with fewer parameters (continuous EQD2T).

2.7.2.c Effect modification

Finally, effect modification by several factors defined *a priori* was assessed. Treatment centre was thought to be an important potential effect modifier as radiotherapy fractionations were known to vary by centre. Additionally, for NSCLC, interaction by receipt of chemotherapy was assessed because of the important interaction seen in the meta-analysis (Chapter 2). For invasive BC, interaction by type of breast surgery was assessed, as surgery is the main treatment for invasive BC. Whether patients received breast conserving surgery or mastectomy could be a strong predictor of patient characteristics and outcomes.

2.7.3 Sensitivity analyses

Sensitivity analyses were conducted to assess the effect of intended versus actual EQD2T in final models obtained for the main questions of interest in this study. If models were similar, it was assumed that intended EQD2T was a good representation both of the policy of prescribed radiotherapy and of the dose actually received by patients. Such an analysis would also be helpful to assess whether patients with implausible recorded information (included in intended EQD2T analyses and excluded from actual EQD2T analyses) were systematically different from other patients in terms of survival and recurrence outcomes. In addition, if results from intended and

actual EQD2T analyses were similar, assumptions made on average number of treatment days, used to calculate intended EQD2T, could be considered acceptable.

For invasive BC, this sensitivity analysis required calculating both intended and actual EQD2T including boost dose. This is because in actual EQD2T analyses, dates recorded in the data were used as opposed to assumed average treatment time. It was not possible to determine for a given patient when treatment to the whole breast ended and when the boost to just the tumour bed began. For example, patient X received 30 fractions, which is assumed to be 25 fractions to the whole breast plus a tumour bed boost of 5 additional fractions. The total treatment time recorded for patient X was 43 days, though the minimum to maximum number of days needed to complete this treatment depending on the weekday started is 40-42 days. Such a scenario is common in these data, in which there was a wide range of treatment days for many patients for a given fractionation (see page 137). For patient X it is not possible to know whether treatment to the whole breast ended on day 33 or 35 (the norm for patients treated with 25 fractions), or if in fact treatment to the whole breast ended on day 34 or 36. Was it the treatment to the whole breast that took additional time, was there a break between the whole breast treatment and boost, or did the boost take longer than normal? There is no answer in the data.

Thus for invasive BC, two sensitivity analyses were conducted. The first was a comparison of intended EQD2T just to the whole breast and intended EQD2T including boost dose. The second was a comparison of intended EQD2T including boost dose and actual EQD2T (also including boost dose).

Two additional sensitivity analyses were conducted for invasive BC. In the first, breast cancer deaths were censored at age 75, as breast cancer death is known to be over-diagnosed in older patients. In the second, a potential interaction by the presence of any positive lymph nodes was explored.

2.7.4 NSCLC models including patients whose notes were examined

For NSCLC, two further analyses were conducted, incorporating information obtained from examining patient notes in Oxford. The first was to assess the impact of corrections made to existing data based on information in the notes. These corrections had been incorporated in all other analyses, and final models for NSCLC with these corrections were compared to the same models without the corrections.

The second analysis was one which included the new variables obtained from the patient notes and included only those patients whose notes had been examined. A fully adjusted model with categorical intended EQD2T was examined once again, to determine whether new variables obtained from the notes had any confounding effect or independent association with NSCLC. A final model for these patients with and without these new variables was compared to determine the effect of adding these in.

2.7.5 Other Outcomes

Similar models with intended EQD2T and the other outcomes of interest for NSCLC and invasive BC were fitted using the same form of final models obtained for the main questions asked (same co-variates, effect modifiers, and continuous or categorical form of EQD2T).

2.8 Ethical approval

This study was approved on 19 November, 2013, by the National Research Ethics Service (NRES) South Central - Oxford A sub-committee. The study also obtained Research and Development approval (sponsorship) by the Oxford University Hospitals Research and Development Joint Research Office on 7 January, 2014.

3 Results

3.1 Final dataset for analysis (all eligible cancer sites)

Of 73,511 patient records in the CIA dataset, one fourth could be used for an analysis of curative-intent radiotherapy (N=19,654, Figure 4.2). In the four data management and merging steps, records were removed either because of ineligibility or data management issues.

The first step pertained to CIA data eligibility and management. Patients were ineligible because of cancer site, age, type and intent of radiotherapy, availability of information on number of radiotherapy fractions, and different number of fractions to nodes and to the main tumour. Most patients were ineligible either because of their cancer site (N=15,606), palliative intent[6] (N=20,862), or missing number of fractions (N=9,214). Duplicate records were also removed as well as records for which no NHS number could be traced[7]. In all, 23,737 CIA records were available for a merge with CAS data.

The second step dealt with CAS data management and a match with the CIA data. Records were removed because they were duplicates (N=84) or there was no information on cancer site (N=983). 174 records for patients with bilateral invasive BC were also removed. 20,486 of the remaining patients were successfully matched between CAS and CIA on cancer site and dates. 1,255 second primary cancers were identified.

The third step encompassed merges with other data and an update of the CAS data. Ten Leicester NSCLC patients were added from the Trent CIA dataset. In all, 20,124 patients remained in the dataset after merges with other PHE data sources. Encouragingly, only nine patients were further removed during an update of the CAS data just prior to preparing data for analyses. An additional 481 second primary cancers were identified.

[6] The extent of patients treated with palliative intent can be assessed by examining numbers of patients treated with fewer than ten fractions in the initial dataset (Table 3.1).
[7] Though initially 19,248 patients were missing NHS numbers, through multiple waves of tracing, these numbers could be reduced to only 252 of eligible patients.

During the process of creating variables for analytical purposes and of examining data in more detail (fourth step), 51 breast cancer patients were removed due to the type of radiotherapy fractionation they received following mastectomy[8]. 410 patients were removed as their radiotherapy start date was recorded as having occurred over a year after the diagnosis date. The final dataset contained 19,654 patients, of whom 1,704 had at least one second primary cancer. Patients in this final dataset were tabulated by cancer site and number of fractions (Table 4.5).

Further site-specific patient exclusions for NSCLC, invasive BC, and DCIS are listed (Figure 4.3). Of 350 NSCLC patients eligible for analyses, it was decided to exclude 19 patients with Pancoast tumours, as many of these have better prognosis than other NSCLC patients not eligible for surgery (this was the case also in my data, results not shown). From the Oxford patient notes project, seven patients were found to have been treated with high-dose palliative intent and were excluded from analyses. Of 10,929 breast and DCIS patients, a total of 1,573 were further excluded from analyses, primarily because of missing information on type of surgery (N=967). 168 patients were excluded because, within three months of diagnosis, they had died, departed from the United Kingdom, had contralateral or lymph node cancer, had metastases or palliative treatment, or had a recurrence in an unknown location. A further 239 patients were excluded because they died within three months of the end of radiotherapy treatment. Many of these 407 patients were likely to have had metastatic disease at the time of diagnosis.

3.2 Non-small cell lung cancer

3.2.1 Descriptive analyses

Assumed radiotherapy fractionations based on numbers of fractions recorded in CIA data are presented separately by treatment centre (Table 4.3). Standard numbers of fractions were 20, 30, 32, 33, and 36. Patients who received non-standard numbers of fractions are also shown, with an

[8] Mastectomy patients who received any radiotherapy boost were excluded (N=43), as were mastectomy patients in Mount Vernon who received 20 fractions (a palliative course in Mount Vernon).

Table 4.5: Final dataset: Number of patients receiving each number of radiotherapy fractions, by cancer site

No. fractions	Breast	DCIS	NSCLC	SCLC/ Undefined lung	Head and Neck	Brain	Oesophagus	Stomach	Prostate	Rectum	Anus	Vagina	Uterus	Cervix	Bladder	Hodgkin Lymphoma	Nonfollicular lymphoma	Total
4										4								**4**
5										267								**267**
6										3								**3**
9										1								**1**
10										9	1							**10**
11	13	1								1						2		**17**
12	336	3				6				9	1						1	**356**
13	1,410	26				3				2								**1,441**
14	7									2								**9**
15	2,067	149		119			12	1	23	3	1	3	2	5	4	47	23	**2,459**
16	815	5	1	1		3	1		6				1	1	1		2	**837**
17	21		2	1	6	2	1		6						1	6	2	**48**
18	1,105	27	1	3	7	2	1		12	3			1	1	1	2	7	**1,173**
19	25	1	3	3	3	1	2		135	1	1					2	1	**178**
20	2,136	99	178	42	260	18	33		1,691	8	3	5	50	1	212	40	45	**4,821**
21	8		4		2	3			5	2			1					**25**
22	5	2		1	2	3	3			5	2	2	1	1		1	3	**31**
23	111	8	1	1	1	3	1		16	3		1	1	1				**148**
24	24	1			3		1		1	8		1	2	1	1			**43**
25	1,506	151	11	17	19	12	155	6	24	647	34	17	394	93	12		2	**3,100**
26	9	2	2	1		3	3			3	1		2	1				**27**
27	6		3	1	7	2	1		3	4	6	2	48	6	1		1	**91**
28	65	9	1	1	3	11	20	2	5	161	149	9	11	111	2	1		**561**
29	20	1		1	8	4	1		3	2	2	4	1	2				**49**
30	724	4	24	9	424	428	4		45	42	4	8	4	19	3	1		**1,743**
31	10				9	4	1		8				2					**34**
32	4		19	6	45	8	3		263	2	1	4	1	2	19	1		**378**
33	8		10	4	332	4	1		91			6	7	8	19			**490**
34					14				13			3		2				**32**
35	2		1		26				544			3	4	5	4			**589**
36	2		88	9	5				8			2		4				**118**
37	1				1	1			542			2		1				**548**
38					1				5				1	1				**8**
39					6				3									**9**
40			1		3													**4**
50							1											**1**
75					1													**1**
Total	**10,440**	**489**	**350**	**220**	**1,188**	**521**	**245**	**9**	**3,452**	**1,192**	**206**	**72**	**534**	**266**	**280**	**103**	**87**	**19,654**

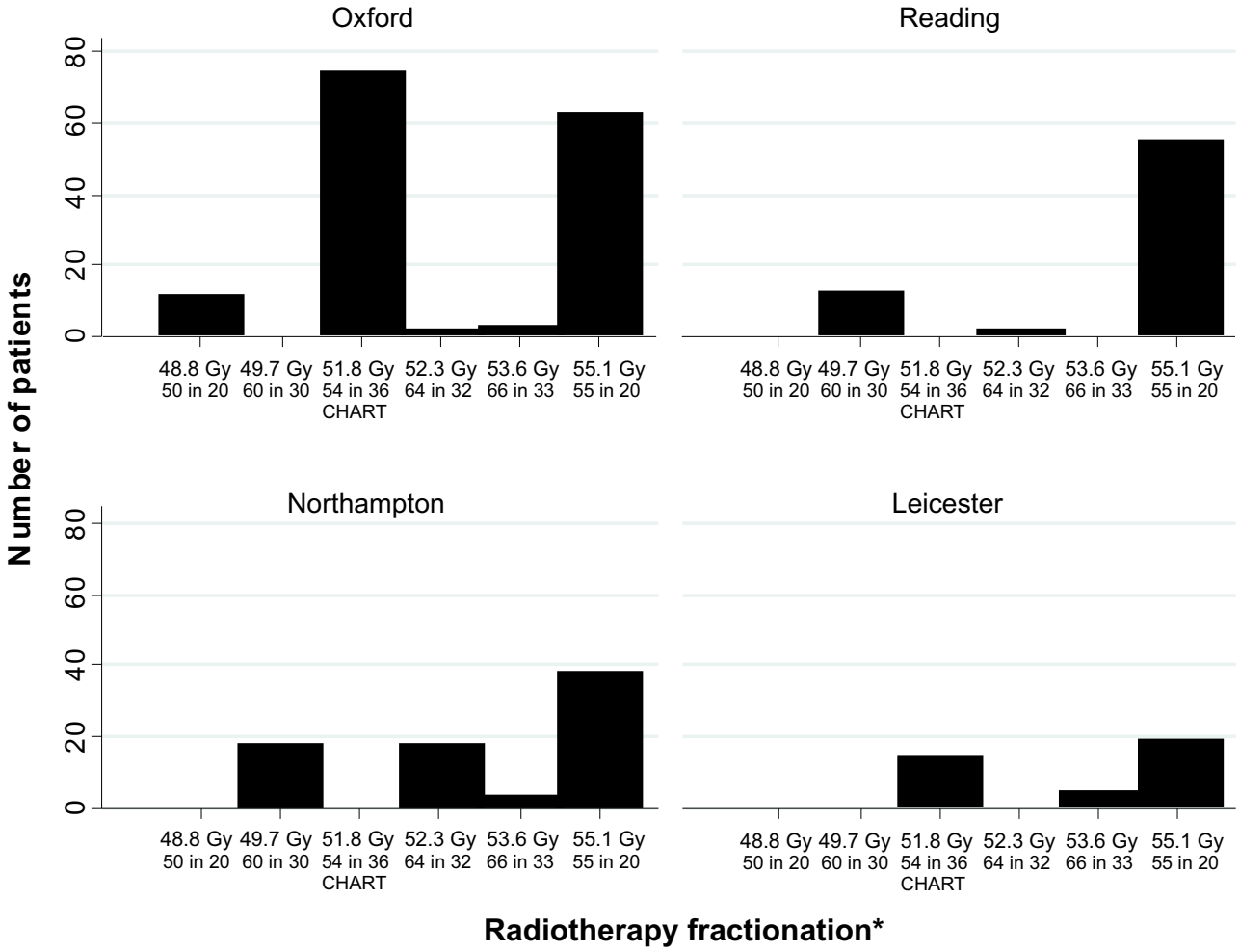
indication of the assumed intended fractionation for their non-standard number of fractions. Of the 324 NSCLC patients included in analyses, 14 had a record of having received a non-standard number of radiotherapy fractions (numbers in blue and italics). Reading had the highest proportion with a record of non-standard fractions (8/66 patients, 12%).

As expected, there was variability in the fractionations given by treatment centre (Figure 4.4). All centres gave 55 Gy in 20 fractions, while CHART was only given in Oxford and Leicester. The international standard for treating inoperable, locally advanced NSCLC was 60 Gy in 30 daily fractions (4), but this was only given in Reading and Northampton. Fractionations also varied over calendar period (Figure 4.5). The proportion of patients receiving 55 Gy in 20 fractions increased over time, while numbers receiving CHART decreased. In 2010-11, only one patient received CHART. The proportion of patients given 60 Gy in 30 remained stable over time. The number of days in which patients received a given intended EQD2T varied considerably for all patients except those receiving CHART (Figure 4.6). For example, for patients intended to receive 55 Gy in 20 fractions the range of recorded treatment time was 1 to 83 days.

Using the EQD2T formula in Chapter 2 (see page 31), the lowest intended dose was calculated to be 50 Gy in 20 fractions at 48.8 Gy and the highest dose 55 Gy in 20, at 55.1 Gy. CHART was at the lower middle end of the range at 51.8 Gy, and the conventional 60 Gy in 30 fractions was calculated to be 49.7 Gy.

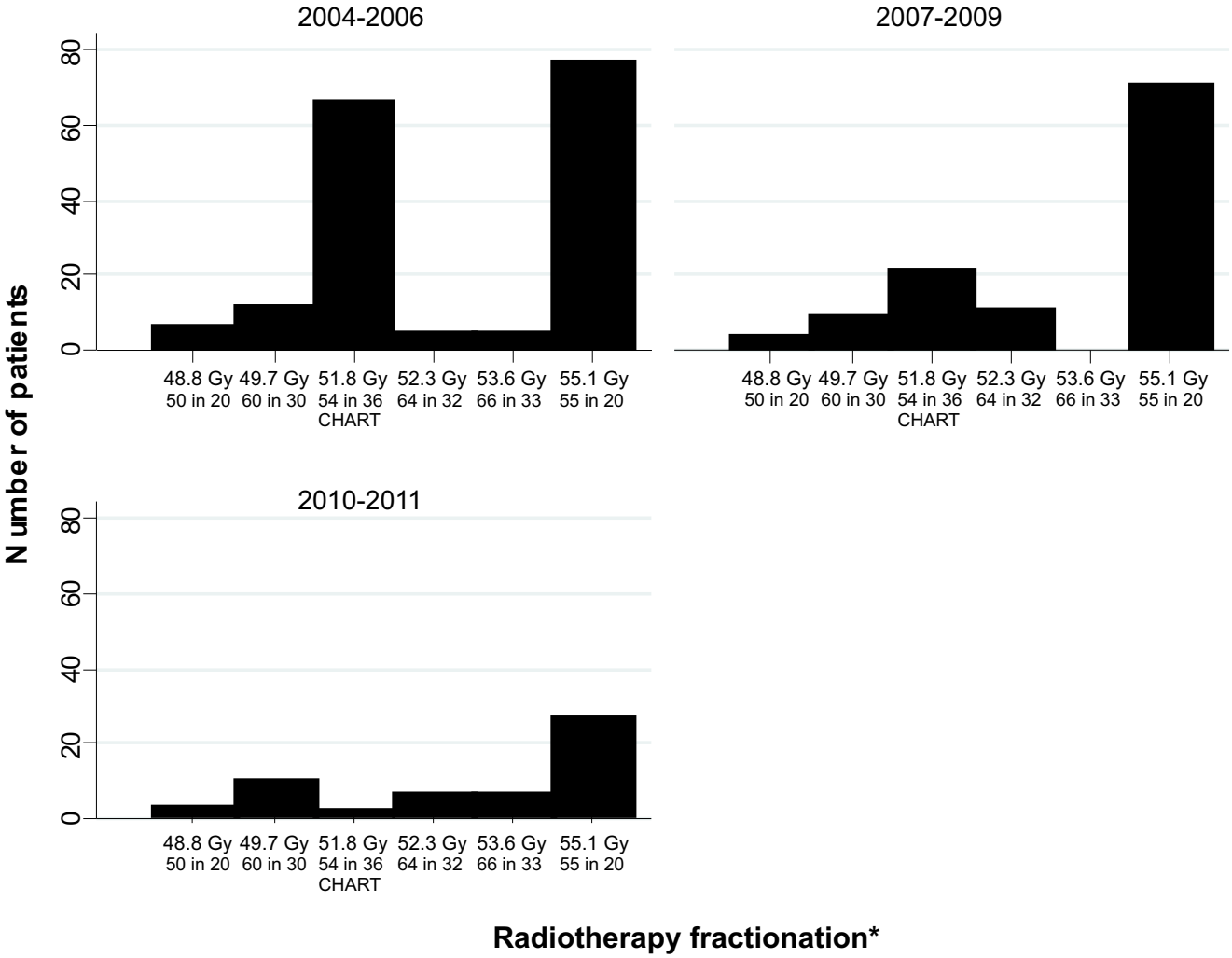
By 31 December, 2016, 94% (303/324) of NSCLC patients had died and 81% (262/324) had died of lung cancer, with a mean follow-up time of 2.9 years (standard deviation 2.7 years, range 1.1 months to 12.4 years, Table 4.6, Panel A). By 30 April, 2016, seven percent (22/324) of patients had developed second primary cancers, with a mean follow-up time of 2.4 years (standard deviation 2.0 years, range 1.1 months to 9.9 years).

Half of patients (172/324) received 55 Gy in 20 fractions and a quarter (86/324) received 54 Gy in 36 fractions, CHART (Table 4.6). Oxford patient notes revealed that ten patients thought to have



* EQD2T indicated in top line, total dose and number of fractions indicated in bottom line.
Abbreviations: EQD2T=equivalent dose in 2 Gy fractions corrected for time. CHART=continuous hyperfractionated accelerated radiotherapy.

Figure 4.4: Number of NSCLC cancer patients treated by radiotherapy fractionation at each treatment centre.



* EQD2T indicated in top line, total dose and number of fractions indicated in bottom line.
Abbreviations: EQD2T=equivalent dose in 2 Gy fractions corrected for time. CHART=continuous hyperfractionated accelerated radiotherapy.

Figure 4.5: Number of NSCLC patients treated by radiotherapy fractionation over calendar period.

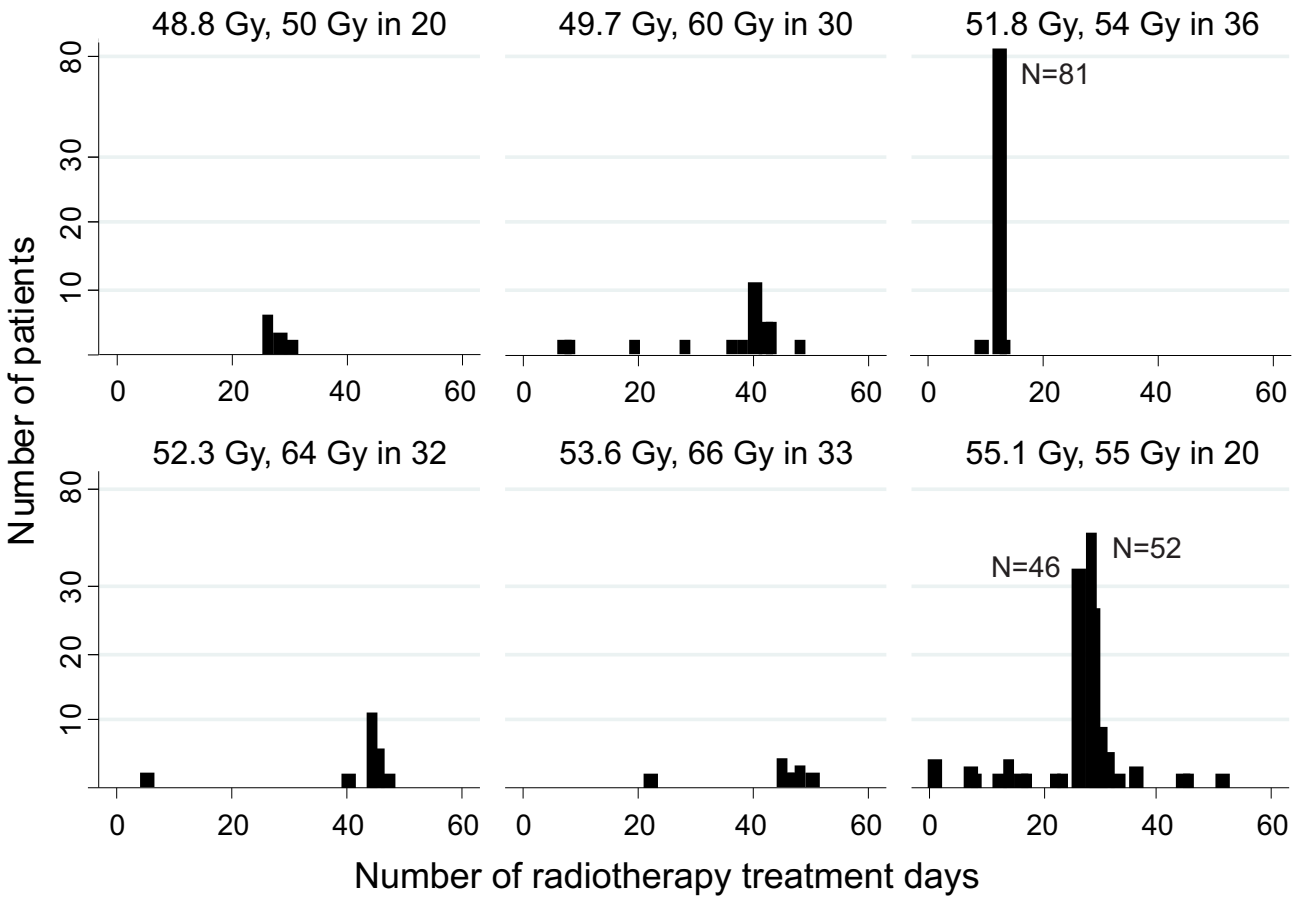


Figure 4.6: Number of NSCLC patients treated by number of treatment days for each radiotherapy fractionation. Data for patients with more than 60 treatment days are not displayed.

Table 4.6: Descriptive characteristics of lung patient population

	Total no. patients	Mean (SD)	Death from lung cancer %	p*	Any death %	p*	2nd primary cancers %	p*	Intended EQD2T p*
A. All patients									
Total	**324**		**81**		**94**		**7**		-
Follow-up time (years)									
Any death		2.9 (2.7)							
Second cancers		2.4 (2.0)							
Intended EQD2T (Gy), Total dose (Gy) in no. fractions									
48.8 , 50 in 20	10	53.4 (2.1)	70	0.8	100	0.4	0	0.4	-
49.7, 60 in 30	28		86		93		7		
51.8, 54 in 36	86		79		98		12		
52.3, 64 in 32	19		74		89		5		
53.6, 66 in 33	9		78		89		11		
55.1, 55 in 20	172		83		92		5		
Grouped actual EQD2T (Gy)									
35.0-51.5	29	53.3 (2.0)	79	0.6	93	0.6	7	0.5	-
51.8	83		78		98		12		
52.0-53.9	31		74		90		6		
54.0-54.9	80		84		95		5		
55.0-56.0	45		87		93		7		
Treatment centre									
Oxford	148		81	0.09	95	0.6	7	0.03	<0.001
Reading	66		83		91		2		
Northampton	75		85		93		7		
Leicester	35		66		91		17		
Age (years)									
38-58	62	68.1 (10.0)	84	0.9	89	0.2	3	0.4	<0.001
59-64	63		81		90		5		
65-70	63		81		94		10		
71-77	69		81		97		6		
78-92	67		78		97		10		
Sex									
Male	194		82	0.5	96	0.01	8	0.2	0.5
Female	130		79		89		5		
Social deprivation (quintiles of IMD score)									
Least deprived	122		78	0.8	90	0.4	7	0.8	0.8
2nd	72		82		96		10		
3rd	51		82		94		4		
4th	53		81		96		6		
Most deprived	26		88		96		8		
Tumour laterality									
Left	136		80	0.9	94	0.7	8	0.7	<0.001
Right	151		81		92		7		(0.5[†])
Central	1		100		100		0		
Missing	36		83		97		3		

Table continued on next page.

Table 4.6 continued

	Total no. patients	Mean (SD)	Death from lung cancer %	p*	Any death %	p*	2nd primary cancers %	p*	Intended EQD2T p*
A. All patients continued									
Cytotoxic chemotherapy									
None	193		76	0.009	95	0.2	9	0.03	<0.001
Any	131		88		92		3		
Surgery									
None	306		81	0.3	94	0.4	7	0.2	0.02
Any	18		72		89		0		
Calendar period									
2004-2006	165		77	0.07	94	0.6	9	0.2	<0.001
2007-2009	111		82		92		5		
2010-2011	48		92		96		4		
Stage (CAS dataset)									
1	10			-		-		-	-
2	4								
3	28								
4	5								
Missing	277								
B. Data from Oxford patients notes									
Total	**114**		**81**		**94**		**4**		-
Stage									
1	35		74	0.4	97	0.7	3	0.8‡	<0.001
2	22		77		95		0		
3	51		86		90		4		
4	4		100		100		0		
Missing	2		50		100		50		
Smoking status at diagnosis									
Never smoked	5		40	0.04§	80	0.4§	0	0.9§	0.6§
Ex-smoker	63		78		94		3		
Current smoker	40		88		95		3		
Missing	6		100		100		17		
History of serious comorbidity¦									
None	76		82	0.7	92	0.3	4	0.7	0.05
Any	38		79		97		3		
Timing of cytotoxic chemotherapy									
None	69		78	0.4	97	0.1	3	0.6	<0.001
Sequential	34		88		91		6		
Any concurrent	11		73		82		0		

* Chi squared test of overall association.
† Test excludes patient with centrally located tumour
‡ Test excludes patients missing data on stage
§ Test excludes patients missing data on smoking status
¦ Ever had serious cardio-vascular of cerebro-vascular disease

Abbreviations: SD=standard deviation. EQD2T=time-corrected equivalent dose in 2 Gy fractions. IMD=Indices of Multiple Deprivation. CAS=Cancer Analysis System. No.=number.

received 55 Gy in 20 fractions had in fact received a total dose of 50 Gy instead. It is therefore possible that some of the patients who received 20 fractions at other centres may also not have received 55 Gy, but that number is unknown.

Using actual rather than estimated treatment dates and excluding patients with non-standard numbers of fractions, the range of actual EQD2T received (35.0-56.0 Gy) was wider than that of intended EQD2T (48.8-55.1 Gy). However, the p-values of association between either measure of EQD2T and any of the three outcomes examined were similar: intended EQD2T and (1) lung cancer death p=0.8, (2) any death p=0.4, (3) second cancers p=0.4; actual EQD2T and (1) lung cancer death p=0.6, (2) any death p=0.6, and (3) second cancers p=0.5.

Most patients were treated in Oxford (N=148) while fewest were treated in Leicester (N=35). This is partly because the Leicester data were only collected up to 2006 in the Thames Valley CIA dataset, and only 10 additional patients could be retrieved for Leicester from the Trent dataset in 2007 and 2008 (no data available thereafter). Treatment centre was weakly associated with lung cancer death (p=0.09) but not associated with death due to any cause (p=0.6). Treatment centre was associated with second cancers (p=0.03), because a surprising 17% of the 35 Leicester NSCLC patients had a record of a second cancer. Treatment centre was strongly associated with intended EQD2T (p<0.001).

The mean age of patients was 68.1 years (standard deviation 10.0 years). Age was not associated with any outcome, but it was strongly associated with intended EQD2T (p<0.001). 60% of patients (194/324) were male. Sex was not associated with either lung-cancer death (p=0.5) or second cancers (p=0.2), nor was it associated with intended EQD2T (p=0.5). Sex was associated with overall survival as more men died (p=0.01). Social deprivation was not associated with any outcome, nor with intended EQD2T.

Tumour laterality was not associated with any outcome, but it was associated with intended EQD2T ($p<0.001$). This result was driven by the single patient whose tumour was located centrally; removing this patient from a test of association resulted in a p-value of 0.5.

Receipt of cytotoxic chemotherapy was strongly associated with lung cancer death ($p=0.009$) and also associated with second cancers ($p=0.03$), but not associated with death due to any cause ($p=0.2$). It was strongly associated with intended EQD2T ($p<0.001$). While patients receiving chemotherapy were more likely to die of lung cancer ($p=0.009$), fewer patients who received chemotherapy died overall ($p=0.2$). Receipt of chemotherapy was associated with serious comorbidity among Oxford patients whose notes were reviewed ($p=0.01$, not shown in table), indicating that fitter patients were selected to receive chemotherapy in addition to radiotherapy.

Fewer patients who received any surgery died of lung cancer or of any cause and none had second cancers, but as only 18/324 patients had surgery, none of the p-values were statistically significant. However, intended EQD2T was associated with surgery ($p=0.02$).

More patients who were irradiated in the most recent calendar period died due to lung cancer ($p=0.07$). Fewer of them had second cancers, though not statistically significant ($p=0.2$). Not surprisingly, calendar period was associated with intended EQD2T ($p<0.001$).

Stage from the CAS dataset could not be used for analyses, due to the high proportion of missing information: 277/324 (85%).

3.2.2 Oxford NSCLC patient notes sub-study

157 patients were recorded as having received their radiotherapy in Oxford. Notes could be retrieved for 124 of them. One additional patient could be identified in the Churchill hospital electronic system, but their notes could not be found in the archive. The remaining patients' records (33/157) could not be traced at all. Notes were available for all of the seven patients still known to be alive at the end of December 2016.

3.2.2.a Missing patient notes

An analysis was conducted to understand which factors were associated with missing notes, to determine what sort of bias missingness might cause. The "missing notes" variable was cross-tabulated and chi squared tests conducted by age at diagnosis, sex, year of diagnosis, initial treatment centre, number of fractions, vital status at the end of 2016, social deprivation, having had a subsequent primary cancer diagnosis, and first two letters of postcode. Not surprisingly, the factor most strongly associated with missing patient notes was treatment year; the longer ago the treatment, the more likely to be missing (Table 4.7). However, neither initial treatment centre nor first two digits of postcode was significantly associated with missingness.

3.2.2.b Incorrect information in the CIA and CAS data

Overall, 18 out of 124 patients (15%) had at least one piece of information corrected or supplemented by checking patient notes:

- Radiotherapy start dates were incorrect for 12 patients
- Stage information was incorrect for 6 of the 14 patients who had any information in CAS
- Laterality was incorrect for two patients
- Curative-intent surgery was incorrect for three patients (they did not have surgery)
- Chemotherapy was incorrect for one patient (they did not have chemotherapy)

In addition, the assumptions made about the intended total dose were incorrect for 16/124 patients, though numbers of fractions had been correctly recorded in the data. One patient who had a record of 23 fractions was originally assumed to have been intended to receive 25 fractions, but in fact this person was intended to receive 54 Gy in 36 fractions. Another patient who had a record of 27 fractions was originally assumed to have been intended to receive 30 fractions, but this person also was intended to receive 54 Gy in 36 fractions. Ten out of 63 patients who received 20 fractions had in fact received 50 Gy total dose rather than the assumed 55 Gy. One

Table 4.7: Missing Oxford lung patients notes, by calendar year and treatment centre (N=124)

	Total no. patients	Missing notes, N(%)	p*
Treatment year			<0.001
2004	29	16 (55)	
2005	29	10 (34)	
2006	28	3 (11)	
2007	18	1 (6)	
2008	28	0 (0)	
2009	12	2 (17)	
2010	13	1 (8)	
Initial treatment centre			0.7
Buckinghamshire Health Trust	60	12 (20)	
Great Western	7	2 (29)	
Horton General	10	4 (40)	
Milton Keynes General	1	0 (0)	
Oxford University	71	14 (20)	
Royal Berkshire	4	0 (0)	
Royal Brompton and Harefield	4	1 (25)	

* Chi squared test of overall association.

patient had actually received 48 Gy in 20 fractions and another 42 Gy in 20 fractions (high dose palliative fractionations).

As a result of corrections to start dates, intended numbers of fractions, and doses, EQD2T calculations were affected. Intended EQD2T changed for 14 of the 124 patients, while of the 120 patients for whom actual EQD2T could be calculated 10 had changes to their calculations.

3.2.2.c Patients found to be ineligible

Overall there were 7/ 124 (6%) patients who were not eligible to be included in the study and who were removed after examining their notes. Three patients received high-dose palliative treatment (two received 20 fractions and another 27), one had an unusual tumour of the trachea, and three received CHART for a recurrence rather than for a primary tumour.

3.2.2.d New variables

New data added from patient notes included both the addition of information that was previously missing and the creation of new variables. Stage data were originally missing for 14/124 patients, and could be retrieved for a further 107 patients, resulting in an overall completeness of this variable of 121/124 (98%). TNM staging was available for 115 of these 121 patients. Stage was derived based on American Joint Committee on Cancer Staging Manual 6th edition for patients diagnosed before 2010, and based on the 7th edition for patients diagnosed later (37, 38). Missing laterality information was retrieved for 15/124 patients, missing radiotherapy start date for 3/124.

Three new variables were created based on information retrieved from patient notes. Comorbidity information was available for 122/124 patients. A comorbidity variable was generated, coded as “yes” if patients had suffered from major cardiovascular or cerebrovascular disease, including ischaemic heart disease, coronary heart disease, valvular heart disease, peripheral heart disease, cardio-vascular disease, myocardial infarction, cerebrovascular disease, and stroke (40/122 patients). A further new variable was whether chemotherapy was not given,

sequential, or concurrent; information was available for all 124 patients. A final variable was smoking status, coded as current (including those who reported smoking up to a month before diagnosis and those still smoking during the treatment course), ex-smoker, and never smoker. 118/124 patients had information available on smoking status. The six patients missing smoking status were excluded from analyses as their outcomes were worse than those of other patients, and they drove results of this variable. In all, 108/124 patients whose notes were reviewed were included in analyses making use of new information.

3.2.2.e Extrapolating findings from 124 patient notes to all 324 NSCLC patients in the study

Within Oxford, it is probable that differences between CAS or CIA data and information in patient notes were similar across cancer sites. Data teams do not work just within one cancer site and would use similar systems to record information for all patients. It is possible that the confusion of high-dose palliative regimens and curative regimens may be present in other cancer sites, but this is less likely to be so for breast cancer, as most breast cancer patients are eligible for treatment of curative intent and present with an earlier cancer stage.

However, it is likely that correctness of CIA and CAS information differs between centres. CAS treatment information has differing degrees of completeness across centres and procedures for data entering and checking are likely to differ between centres. It is therefore not possible to conclude that 15% of NSCLC patients' data in other centres are also likely to have incorrect information. The correctness of CIA and CAS data may also differ according to calendar year. It is possible that data entry for NSCLC patients diagnosed in 2004-2005 in Oxford may differ to that of patients diagnosed 2006-2010, and so the quality of data for Oxford patients whose notes are missing may also differ to that of patients for whom notes were available.

3.2.2.f Associations of new variables with outcomes and intended EQD2T

New variables for the 114 patients whose notes were reviewed and who were treated with curative intent were tabulated and chi squared tests of association conducted by outcomes and intended EQD2T (Table 4.6, panel B). With so few patients, statistical tests were underpowered.

The most commonly recorded stage was III (51/114, 45%), followed by stage I (35/114, 31%). There were no statistically significant associations with any outcomes by stage, though this may be due to the lack of statistical power. Stage was strongly associated with intended EQD2T ($p<0.001$).

Smoking status was the only new variable that showed a statistical association with lung cancer death ($p=0.04$). More than twice the proportion of current smokers died of lung cancer compared to never-smokers (88% versus 40%). Those missing data on smoking status all died of lung cancer and 17% died of second cancers; these six patients were removed from further analyses. There was no association between smoking status and intended EQD2T.

Whether chemotherapy was given sequentially or concurrently with radiotherapy was possible to determine in patients' notes. Patients who received concurrent chemotherapy may have been less likely to die of lung cancer (78% no CT, 88% sequential, 73% concurrent), to die overall (97% no CT, 91% sequential, 82% concurrent), or to have developed second cancers (3% no CT, 6% sequential, 0% concurrent), but none of these associations was statistically significant. Timing of chemotherapy was associated with intended EQD2T ($p<0.001$).

3.2.3 Survival analyses

3.2.3.a Lung cancer survival and intended EQD2T dose

The principle survival analysis for NSCLC consisted of modelling the association between intended EQD2T and lung cancer death. The median lung cancer survival time for patients in the study was 2.14 years (95% CI 1.84-2.31). A Kaplan-Meier plot of lung cancer survival by intended EQD2T

revealed no significant association between the two (p for heterogeneity=0.7, p for trend=0.9, Figure 4.7) and an unadjusted Cox regression model with categorical intended EQD2T showed no association (p=0.7, Table 4.8).

A fully adjusted Cox regression model showed which co-variates were associated with lung cancer survival (Table 4.9). Hazard ratios compare each category of each variable to a baseline level of that variable. In addition to category-specific p-values, a joint likelihood radio test determines the overall association of that variable with lung cancer death. Where applicable, a p-value for linear trend is also presented.

Intended EQD2T as a categorical variable was not significantly associated with lung cancer survival (joint p=0.3, table 4.9). However, patients who received CHART may have been more likely to die of NSCLC than those receiving 55 Gy in 20 fractions (HR 1.38, 95% CI 0.96-1.99, p=0.08). Females were much less likely to die of NSCLC than males (HR 0.68, 95% CI 0.52-0.90, p=0.006). The more recently patients were treated, the more likely they were to die of lung cancer (HR 2007-09 versus 2004-06 1.21, 95% CI 0.90-1.62 and HR 2010-11 versus 2004-06 2.13, 95% CI 1.41-3.20; p=0.002). Age, tumour laterality, social deprivation, chemotherapy, and surgery were not significantly associated with lung cancer survival. There may be an association between social deprivation and lung cancer survival since the hazard ratio appeared to increase with increasing deprivation. However, there were few events in each category, so statistical tests may have been underpowered (p for trend=0.1).

This fully adjusted model was also used to assess confounding, by each co-variate, of the relationship between intended EQD2T and lung cancer survival (Table 4.9). The biggest confounder was calendar period; chemotherapy and sex were also confounders. Age, tumour laterality, level of social deprivation, and receipt of surgery were slight confounders. It was decided not to include laterality in subsequent models, as the effect of laterality was driven by the single patient with a centrally located tumour.

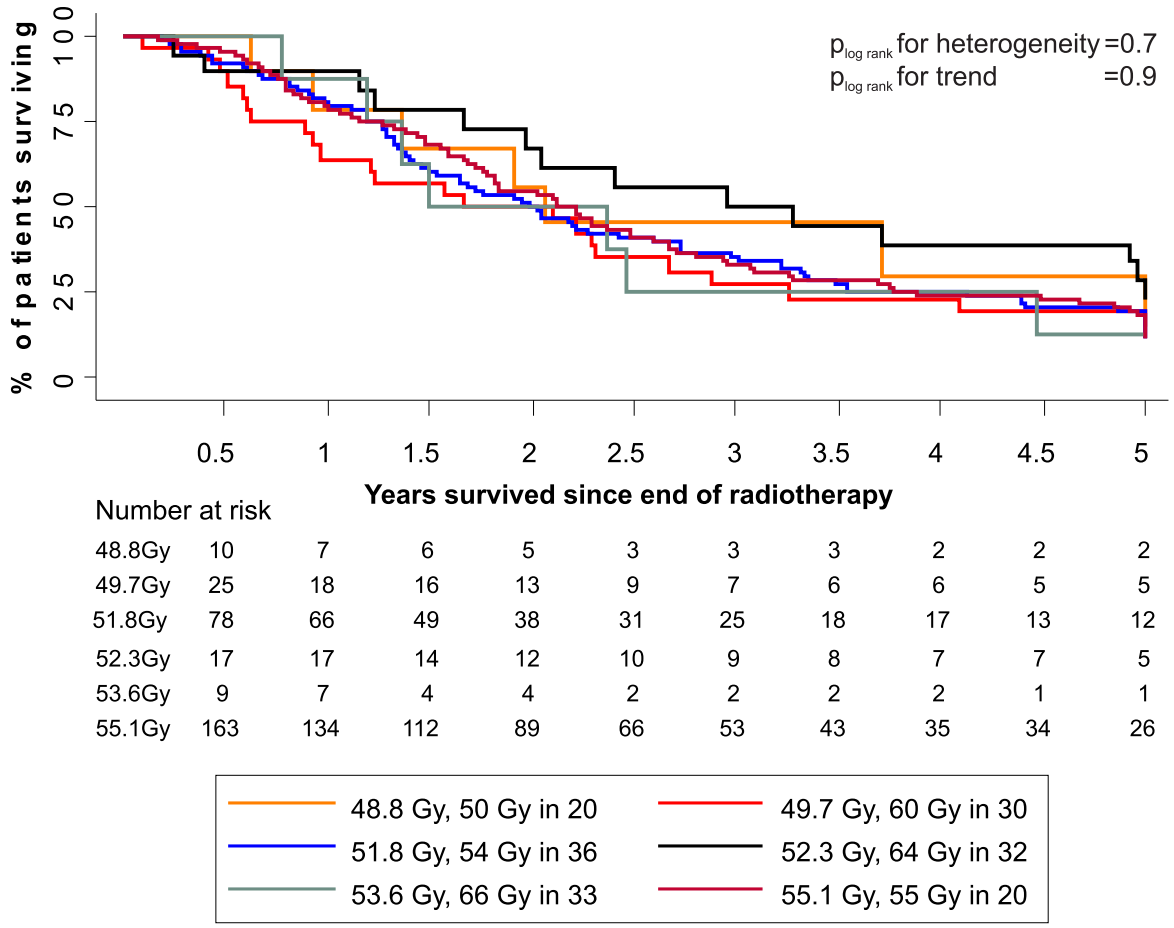


Figure 4.7: Lung cancer survival by intended EQD2T (N=324)

Table 4.8: Lung cancer survival, unadjusted (N=324)

EQD2T (Gy)	Total dose (Gy) in no. fractions	No. events/ patients	HR	SE	95% CI	p_{Wald}*	Joint p_{LR}†
48.8	50 in 20	7/10	0.86	0.33	(0.40, 1.85)	0.7	0.7
49.7	60 in 30	24/28	1.17	0.26	(0.76, 1.80)	0.5	
51.8	54 in 36 (CHART)	68/86	1.04	0.15	(0.78, 1.39)	0.8	
52.3	64 in 32	14/19	0.69	0.19	(0.40, 1.19)	0.2	
53.6	66 in 33	7/9	1.04	0.40	(0.49, 2.23)	0.9	
55.1	55 in 20	142/172	1				

* Wald test of association with outcome, separately for each category of EQD2T, on one degree of freedom.
† Joint likelihood ratio test of association with outcome, of EQD2T variable including all six categories, on five degrees of freedom.

Abbreviations: LC=lung cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number

Table 4.9: Lung cancer survival, adjusted for all available factors and indicating degree of confounding (N=324)

		No. events/ patients	HR	SE	95% CI	p_{Wald}*	Joint p_{LR}†	p_{Wald} trend‡	Degree of confounding§
EQD2T (Gy)	**Total dose (Gy) in no. fractions**								
48.8	50 in 20	7/10	0.85	0.37	(0.36, 2.00)	0.7	0.3	0.9	-
49.7	60 in 30	24/28	0.87	0.21	(0.55, 1.40)	0.6			
51.8	54 in 36 (CHART)	68/86	1.38	0.26	(0.96, 1.99)	0.08			
52.3	64 in 32	14/19	0.63	0.19	(0.35, 1.12)	0.1			
53.6	66 in 33	7/9	0.79	0.32	(0.36, 1.76)	0.6			
55.1	55 in 20	142/172	1						
Age (years)									Slight
38-58		52/62	1.07	0.23	(0.70, 1.62)	0.8	0.8	-	
59-64		51/63	0.81	0.18	(0.53, 1.25)	0.3			
65-70		51/63	1						
71-77		56/69	0.95	0.20	(0.63, 1.43)	0.8			
78-92		52/67	0.92	0.21	(0.59, 1.43)	0.7			
Sex									Moderate
Male		159/194	1						
Female		103/130	0.68	0.09	(0.52, 0.90)	0.006	-	-	
Tumour laterality									Slight¦
Left		109/136	1				0.2	-	
Right		122/151	0.92	0.13	(0.70, 1.20)	0.5			
Central		1/1	15.06	16.85	(1.68, 134.85)	0.02			
Missing		30/36	1.22	0.28	(0.78, 1.92)	0.4			
Social deprivation (quintiles of IMD score)									Slight
Least deprived		95/122	1				0.3	0.1	
2nd		59/72	1.37	0.24	(0.97, 1.95)	0.07			
3rd		42/51	1.21	0.24	(0.82, 1.78)	0.3			
4th		43/53	1.21	0.24	(0.82, 1.79)	0.3			
Most deprived		23/26	1.55	0.39	(0.95, 2.52)	0.08			
Calendar period									Major
2004-2006		127/165	1				0.002	0.001	
2007-2009		91/111	1.21	0.18	(0.90, 1.62)	0.2			
2010-2011		44/48	2.13	0.44	(1.41, 3.20)	<0.0001			
Cytotoxic Chemotherapy									Moderate
None		147/193	1				-	-	
Any		115/131	1.19	0.22	(0.84, 1.70)	0.3			
Surgery									Slight
None		249/306	1				-	-	
Any		13/18	0.68	0.21	(0.37, 1.25)	0.2			

* Wald test of association with outcome, separately for each category of variable, on one degree of freedom.
† Joint likelihood ratio test of association with outcome, of variable including all *n* categories, on (*n* -1) degrees of freedom.
‡ Wald test for linear trend across variable.
§ Degree of confounding was assessed by examining this full model with a model excluding each of the potential confounders, one by one. See Methods for detailed explanation.
¦ Laterality was considered to be a problematic variable in these analyses, because the single patient with a central tumour and the many with missing information appeared to be driving the effect of laterality. As it was only a slight confounder, laterality was removed from subsequent models.

Abbreviations: LC=lung cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number. IMD=Indices of Multiple Deprivation.

A series of models including relevant confounders was fitted, with and without effect modifiers (Table 4.10). In models fitting intended EQD2T as a continuous variable, hazard ratios indicate the increase in hazard per unit Gray increase in intended EQD2T. In a model fitting intended dose as a continuous variable without effect modifiers, there was no significant trend in hazard of lung cancer death (HR 0.99, 95% CI 0.93-1.05, p=0.8, Model 1). However, treatment centre had a highly significant interaction effect, meaning that the trend in hazard of lung cancer death differed by centre (p=0.0007, Model 2). In Oxford and Leicester, there may have been a slight decrease in hazard of lung cancer death with increasing intended EQD2T (HR 0.94, 95% CI 0.86-1.04, p=0.2, and HR 0.93, 95% CI 0.71-1.22, p=0.6 respectively). However in Reading there appeared to be a definite decrease in hazard of lung cancer death with increasing intended EQD2T (HR 0.83, 95% CI 0.74-0.95, p=0.005) while in Northampton the opposite was true (HR 1.20, 95% CI 1.06-1.36, p=0.004).

There was also an interaction by whether or not chemotherapy was given (p=0.02, Model 3). This was not surprising given the interaction by chemotherapy shown in the meta-analysis (Chapter 2). Similarly to the meta-analysis, there was an *increase* in survival the higher the intended EQD2T among patients who were not given chemotherapy (HR 0.91, 95% CI 0.83-1.00, p=0.05), and a possible *decrease* in survival with higher intended EQD2T among patients who were given chemotherapy (HR 1.05, 95% CI 0.97-1.15, p=0.2)[9].

Including simultaneous effect modification by centre and chemotherapy showed a better fit to the data than just the interaction by chemotherapy alone (p=0.006, Model 4, compared to p=0.02, Model 3). This model presents effects of increasing dose separately by whether or not chemotherapy was given, in each of the centres. It permits the comparison separately within each centre of the trend in hazard among patients who did not receive chemotherapy versus those who did. In each comparison within centre, patients who received chemotherapy had a worse hazard of death with increasing dose than patients who did not receive chemotherapy. For

[9] An increase in survival corresponds to a decrease in the hazard of death, and vice versa.

Table 4.10: Lung cancer survival, continuous and categorical intended radiotherapy dose, and effect modifiers (N=324)*

EQD2T (Gy)	Level of effect modification		No. events/ patients	HR	SE	95% CI	p_{Wald} †	p_{LR} ‡ test comparing this model to Model 1
Model 1: Continuous model for dose								
Trend per Gy			262/324	0.99	0.03	(0.93, 1.05)	0.8	-
Model 2: Effect modification by treatment centre								
Trend per Gy	Oxford		120/148	0.94	0.05	(0.86, 1.04)	0.2	0.0007
	Reading		55/66	0.83	0.05	(0.74, 0.95)	0.005	
	Northampton		64/75	1.20	0.08	(1.06, 1.36)	0.004	
	Leicester		23/35	0.93	0.13	(0.71, 1.22)	0.6	
Model 3: Effect modification by chemotherapy								
Trend per Gy	No CT		147/193	0.91	0.04	(0.83, 1.00)	0.05	0.02
	Any CT		115/131	1.05	0.04	(0.97, 1.15)	0.2	
Model 4: Effect modification by both chemotherapy and treatment centre								
Trend per Gy	Oxford	No CT	72/93	0.91	0.08	(0.77, 1.08)	0.3	0.006
		Any CT	48/55	0.97	0.06	(0.85, 1.10)	0.6	
	Reading	No CT	29/38	0.81	0.08	(0.66, 0.99)	0.04	
		Any CT	26/28	0.88	0.08	(0.74, 1.04)	0.1	
	Northampton	No CT	25/29	1.05	0.14	(0.82, 1.36)	0.7	
		Any CT	39/46	1.21	0.09	(1.04, 1.41)	0.01	
	Leicester	No CT	21/33	0.93	0.13	(0.71, 1.22)	0.6	
		Any CT§	2/2					
Model 5: Categorical model for dose EQD2T (Gy), Total dose (Gy) in no. fractions								
48.8 , 50 in 20			7/10	0.94	0.38	(0.42, 2.07)	0.9	0.2
49.7, 60 in 30			24/28	0.91	0.22	(0.57, 1.45)	0.7	
51.8, 54 in 36 (CHART)			68/86	1.37	0.25	(0.95, 1.95)	0.09	
52.3, 64 in 32			14/19	0.62	0.18	(0.35, 1.11)	0.1	
53.6, 66 in 33			7/9	0.87	0.34	(0.40, 1.89)	0.7	
55.1, 55 in 20			142/172	1				
Models without changes made from Oxford patient notes project:								
Model 1a: Model 1 without changes								
Trend per Gy			262/324	0.97	0.03	(0.91, 1.04)	0.4	-
Model 4a: Model 4 without changes								
Trend per Gy	Oxford	No CT	71/91	0.80	0.06	(0.70, 0.92)	0.002	-
		Any CT	49/57	0.89	0.16	(0.63, 1.27)	0.5	
	Reading	No CT	29/38	0.82	0.08	(0.67, 1.00)	0.05	
		Any CT	26/28	0.87	0.07	(0.74, 1.03)	0.1	
	Northampton	No CT	25/29	1.05	0.13	(0.82, 1.35)	0.7	
		Any CT	39/46	1.22	0.10	(1.04, 1.42)	0.01	
	Leicester	No CT	21/33	0.94	0.13	(0.71, 1.24)	0.7	
		Any CT§	2/2					

*All models were adjusted for chemotherapy yes/no, surgery, grouped age, sex, social deprivation trend, and trend across calendar period.

† Wald test of association with outcome, separately for each category of variable, on one degree of freedom.

‡ Likelihood ratio test comparing more complex model with simpler model.

§ Hazard ratio could not be estimated due to insufficient number of patients.

Abbreviations: LC=lung cancer. HR=hazard ratio. SE=standard error. CI=confidence interval. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number

example, among Oxford patients who did not receive chemotherapy, the hazard ratio per Gy increase in intended EQD2T was 0.91 (95% CI 0.77-1.08, p=0.3) and among those who received chemotherapy it was 0.97 (95% CI 0.85-1.10, p=0.6). In Oxford, there may have been a benefit associated with higher radiotherapy dose in both groups regardless of whether or not chemotherapy was given, though the trends were not statistically significant. There may also have been a benefit of higher radiotherapy dose in Leicester, though again this was not statistically significant (No Chemotherapy: HR 0.93, 95% CI 0.71-1.22, p=0.6). In Reading, there may also have been a benefit of higher radiotherapy dose, but this was only statistically significant among patients who did not receive chemotherapy (No chemotherapy: HR 0.81, 95% CI 0.66-0.99, p=0.04 versus Chemotherapy: HR 0.88, 95% CI 0.74-1.04, p=0.1). Conversely, in Northampton, there was an *increase* in hazard of lung cancer death with increasing intended EQD2T, and this was statistically significant among patients who received chemotherapy (No chemotherapy: HR 1.05, 95% CI 0.82-1.36 versus Chemotherapy: HR 1.21, 95% CI 1.04-1.41, p=0.01).

To summarise, in Model 4, hazards among patients with chemotherapy were consistently higher than among those without chemotherapy. However, the underlying effect of higher intended EQD2T differed by treatment centre, regardless of whether chemotherapy was given. In some centres, the effect of higher intended EQD2T was a reduction in hazard, while in others it was an increase in hazard. There were not many patients in any of these categories, and measuring the effects within any given category was likely to be very underpowered. In Leicester there were only two patients who received chemotherapy and no effect could be estimated. However, overall, the heterogeneity between these groups was sufficient to produce a highly significant improvement in fit comparing this model to a simpler one without interactions (Model 4 versus Model 1).

Model 5 shows that fitting intended EQD2T as a categorical variable was not as good a fit to the data as the simpler model with continuous EQD2T (p=0.2) and thus all further models examined were with dose as continuous.

3.2.3.b Analysis using additional variables from Oxford patient notes

A separate analysis for lung cancer survival was conducted for Oxford patients whose notes were available (N=108). As was done for all patients, a fully adjusted model was examined for degree of confounding of all variables included in the final models above, as well as the additional variables obtained (Table 4.11). Calendar period was still the strongest confounder in this model, and the new chemotherapy variable and sex were also confounders, as above. Age and social deprivation were stronger confounders than previously, and the three new variables smoking status, cancer stage, and history of serious comorbidity were also confounders. Surgery remained only a slight confounder. The overall p-value for the effect of intended EQD2T was more significant than that in the model with all centres (p=0.1 in Table 4.11 versus p=0.3 in Table 4.9), however confidence intervals for any given comparison by dose were very wide. The p-value for trend of 0.2 was the same as it was for Oxford in Model 2 (Oxford=top line) in Table 4.10.

There were only 108 patients in this analysis, so there is low statistical power. Nevertheless, sex maintained a weak association with lung cancer survival (p=0.07), and calendar period remained associated (p=0.02). Smoking status at diagnosis was associated with lung cancer survival: current smokers had 1.76 times the hazard of ex- or never-smokers of lung cancer death (95% CI 1.07-2.91, p=0.03). There may also have been an association between stage and lung cancer survival (p for trend=0.1, probably underpowered). There was no association between lung cancer survival and age, social deprivation, chemotherapy, or surgery.

In a continuous model for dose without the new information added from notes, there was no significant trend with increasing dose (HR 0.92, 95% CI 0.81-1.04, p=0.2, Model 1, Table 4.12). Adding in the new information, the hazard ratio remained virtually unchanged (0.91, 95% CI 0.80-1.04, p=0.2, Model 2). An effect modification by chemotherapy was not significant (p=0.9, Model 3).

Table 4.11: Lung cancer survival in Oxford, adjusted for all factors in main model and new factors available through patients notes project. Degree of confounding for each factor is indicated (N=108)

		No. events/ patients	HR	SE	95% CI	p_{Wald}*	Joint p_{LR}†	p_{Wald}‡ trend	Degree of confounding§
EQD2T (Gy)	**Total dose (Gy) in no. fractions**								
48.8	50 in 20	7/10	2.49	3.17	(0.21, 30.09)	0.5	0.1	0.2	-
49.7	60 in 30								
51.8	54 in 36 (CHART)	42/51	4.84	6.45	(0.35, 65.95)	0.2			
52.3	64 in 32	1/1	40.73	74.73	(1.12, 1484.59)	0.04			
53.6	66 in 33	1/1	1.83	2.12	(0.19, 17.8)	0.6			
55.1	55 in 20	35/45	1						
Age (years)									Moderate
38-58		16/20	1.08	0.47	(0.46, 2.54)	0.9	0.96	-	
59-64		18/23	1.07	0.46	(0.46, 2.49)	0.9			
65-70		12/15	1						
71-77		17/21	1.36	0.61	(0.56, 3.28)	0.5			
78-92		23/29	1.29	0.58	(0.53, 3.13)	0.6			
Sex									Moderate
Male		53/65	1				-	-	
Female		33/43	0.59	0.17	(0.34, 1.04)	0.07			
Smoking status at diagnosis									Moderate
Ex/Never		51/68	1				-	-	
Current		35/40	1.76	0.45	(1.07, 2.91)	0.03			
Trend across level of social deprivation (high to low)		86/108	0.92	0.10	(0.75, 1.13)	0.4	-	-	Moderate
Trend across calendar period		86/108	1.86	0.49	(1.11, 3.14)	0.02	-	-	Major
Cancer stage									Moderate
1		25/34	1				0.3	0.1	
2		15/20	1.17	0.47	(0.54, 2.57)	0.7			
3		41/48	2.13	0.80	(1.02, 4.45)	0.04			
4		4/4	1.16	0.88	(0.26, 5.14)	0.8			
Missing		1/2	0.91	0.98	(0.11, 7.52)	0.9			
History of serious comorbidity¦									Moderate
None		57/71	1				-	-	
Any		29/37	1.48	0.47	(0.8, 2.76)	0.2			
Chemotherapy									Moderate
None		52/67	1				0.8	-	
Sequential		26/30	1.38	0.67	(0.53, 3.57)	0.5			
Any concurrent		8/11	1.17	0.83	(0.29, 4.71)	0.8			
Surgery									Slight
None		77/97	1				-	-	
Any		9/11	0.83	0.39	(0.33, 2.08)	0.7			

* Wald test of association with outcome, separately for each category of variable, on one degree of freedom.
† Joint likelihood ratio test of association with outcome, of variable including all *n* categories, on (*n* -1) degrees of freedom.
‡ Wald test for linear trend across variable.
§ Degree of confounding was assessed by examining this full model with a model excluding each of the potential confounders, one by one. See Methods for detailed explanation.
¦ Ever had serious cardio-vascular of cerebro-vascular disease

Abbreviations: LC=lung cancer. HR=hazard ratio. SE=standard error. CI=confidence interval. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number

Table 4.12: Lung cancer death in Oxford patients only: Impact of adding new variables from examination of patient notes. (N=108)

EQD2T (Gy)	Level of effect modification	No. events/ patients	HR	SE	95% CI	p_{Wald}*	p_{LR}† test comparing Model 3 to Model 2
Model 1: Continuous model for dose, same covariates as in Table 4.7‡							
Trend per Gy		86/108	0.92	0.06	(0.81, 1.04)	0.2	-
Model 2: Continuous model for dose, adding new variables obtained from the lung notes project§							
Trend per Gy		86/108	0.91	0.06	(0.80, 1.04)	0.2	-
Model 3: Effect modification by timing of chemotherapy§							
Trend per Gy	No CT	52/67	0.93	0.10	(0.75, 1.15)	0.5	0.9
	Sequential CT	26/30	0.93	0.09	(0.76, 1.13)	0.5	
	Any concurrent CT	8/11	0.86	0.11	(0.68, 1.10)	0.2	

* Wald test of association with outcome, separately for each category of variable, on one degree of freedom.
† Likelihood ratio test comparing more complex model with simpler model.
‡ Model was adjusted for chemotherapy, surgery, grouped age, sex, social deprivation trend, and trend across calendar period.
§ Models were adjusted for timing of chemotherapy, surgery, grouped age, sex, social deprivation trend, trend across calendar period, smoking status, history of comorbidity, and stage.

Abbreviations: LC=lung cancer. HR=hazard ratio. SE=standard error. CI=confidence interval. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number

3.2.3.c Correction of errors in CIA and CAS data

The main model for lung cancer survival was re-run without any corrections to mistakes discovered by examining patient notes, to check the impact these errors had on lung cancer survival results. Results of these re-run models are shown in Table 4.10 to permit comparison between models incorporating corrections and models without corrections. Model 1a in Table 4.10 is a comparison of the model without effect modification. There is little difference in the result (Model 1a: HR 0.97, 95% CI 0.91-1.04 versus Model 1: HR 0.99, 95% CI 0.93-1.05). Model 4a in the same table is a comparison of the final model with effect modification by both centre and chemotherapy: the only change is to results in Oxford. Whereas the hazard ratio in the corrected model for those who did not receive chemotherapy is 0.91 (95% CI 0.77-1.08, Model 4) and for those who did it is 0.97 (95% CI 0.85-1.10, Model 4), previously these would have been 0.80 (95% CI 0.70-0.92, Model 4a) and 0.89 (0.63-1.27, Model 4a), respectively. The reason for these differences is that assumptions made about intended regimens were previously incorrect.

3.2.3.d Lung cancer survival: sensitivity analyses for actual versus intended dose

To compare models of intended and actual EQD2T, intended EQD2T models were restricted to those patients included in actual EQD2T analyses, 268 patients of the original 324 (Table 4.13). Estimates of hazard ratios in continuous *intended* EQD2T models were mostly similar to those including all patients in Table 4.10, though with fewer patients, tests for effect modification were underpowered (Models 2int, 3int, and 4int, Table 4.13). A possible difference between models with all patients versus the reduced models is the estimate of trend with increasing intended EQD2T among patients who did not receive chemotherapy (Model 3int). This trend is not as steep among patients in Table 4.13 (Model 3int, Table 4.13 [N=268]: HR 0.96, 95% CI 0.86-1.07, p=0.5 versus Model 3, Table 4.10 [N=324]: HR 0.91, 95% CI 0.83-1.00, p=0.05).

Table 4.13: Lung cancer survival, other forms of radiotherapy dose: sensitivity analyses (N=268)*

EQD2T (Gy)	Level of effect modification		No. events/ patients	HR	SE	95% CI	p_{Wald} †	p_{LR} ‡ test comparing to simpler model
Model 1int: Intended EQD2T dose, but only for those patients included in the actual EQD2T analysis								
Trend per Gy			217/268	1.01	0.04	(0.94, 1.08)	0.8	-
Model 2int: Model 1 with effect modification by treatment centre								Comparing to Model 1int
Trend per Gy	Oxford		113/141	0.94	0.05	(0.84, 1.04)	0.2	0.03
	Reading		28/31	0.85	0.10	(0.67, 1.07)	0.2	
	Northampton		58/68	1.19	0.08	(1.04, 1.36)	0.01	
	Leicester		18/28	0.96	0.14	(0.72, 1.29)	0.8	
Model 3int: Model 1 with effect modification by chemotherapy								Comparing to Model 1int
Trend per Gy	No CT		126/164	0.96	0.05	(0.86, 1.07)	0.5	0.2
	Any CT		91/104	1.05	0.05	(0.95, 1.15)	0.4	
Model 4int: Model 1 with effect modification by both chemotherapy and centre								Comparing to Model 1int
Trend per Gy	Oxford	No CT	69/90	0.92	0.08	(0.77, 1.10)	0.4	0.3
		Any CT	44/51	0.95	0.07	(0.83, 1.09)	0.4	
	Reading	No CT	17/20	0.92	0.08	(0.77, 1.10)	0.4	
		Any CT	11/11	0.91	0.12	(0.70, 1.16)	0.4	
	Northampton	No CT	24/28	1.07	0.14	(0.82, 1.38)	0.6	
		Any CT	34/40	1.19	0.10	(1.00, 1.42)	0.05	
	Leicester	No CT	16/26	0.96	0.15	(0.71, 1.29)	0.8	
		Any CT	2/2§					
Model 1act: Actual EQD2T dose, calculated using data on treatment dates and including only patients with plausible information on number of fractions and radiotherapy treatment dates								
Trend per Gy			217/268	1.01	0.04	(0.95, 1.09)	0.7	-
Model 2act: Model 1act with effect modification by treatment centre								Comparing to Model 1act
Trend per Gy	Oxford		113/141	0.95	0.05	(0.85, 1.06)	0.3	0.01
	Reading		28/31	0.81	0.10	(0.63, 1.04)	0.1	
	Northampton		58/68	1.21	0.08	(1.05, 1.38)	0.007	
	Leicester		18/28	0.93	0.15	(0.68, 1.26)	0.6	
Model 3act: Model 1act with effect modification by chemotherapy								Comparing to Model 1act
Trend per Gy	No CT		126/164	0.97	0.05	(0.87, 1.08)	0.5	0.2
	Any CT		91/104	1.05	0.05	(0.96, 1.16)	0.3	
Model 4act: Model 1act with effect modification by both chemotherapy and centre								Comparing to Model 1act
Trend per Gy	Oxford	No CT	69/90	0.96	0.08	(0.80, 1.14)	0.6	0.1
		Any CT	44/51	0.95	0.07	(0.82, 1.10)	0.5	
	Reading	No CT	17/20	0.61	0.27	(0.25, 1.46)	0.3	
		Any CT	11/11	0.89	0.13	(0.67, 1.19)	0.4	
	Northampton	No CT	24/28	1.08	0.13	(0.84, 1.37)	0.6	
		Any CT	34/40	1.22	0.11	(1.03, 1.46)	0.02	
	Leicester	No CT	16/26	0.93	0.15	(0.68, 1.28)	0.7	
		Any CT	2/2§					

* All models were adjusted for chemotherapy yes/no, surgery, grouped age, sex, social deprivation trend, and trend across calendar period.

† Wald test of association with outcome, separately for each category of variable, on one degree of freedom.

‡ Likelihood ratio test comparing more complex model with simpler model.

§ Hazard ratio could not be estimated due to insufficient number of patients.

Abbreviations: LC=lung cancer. HR=hazard ratio. SE=standard error. CI=confidence interval. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number.

Analyses for *actual* EQD2T presented in Models 1act to 4act compare with intended EQD2T analyses in Models 1int to 4int (Table 4.13). Results are consistent between actual and intended EQD2T for each model number.

3.2.3.e Other outcomes

In addition to lung cancer survival, associations were examined between increasing intended EQD2T dose and (1) overall survival and (2) hazard of developing a second primary cancer (Table 4.14).

Results for overall survival are presented in Models 1os-4os, results for second cancers in Models 1sc-3sc. Where possible, the same types of models are presented for each of these analyses as were presented for the main lung cancer survival analyses in Table 4.13: continuous intended EQD2T without effect modification (Models 1os and 1sc), effect modification by centre (Models 2os and 2sc), effect modification by chemotherapy (Models 3os and 3sc) and effect modification by both centre and chemotherapy (Model 4os, analysis not possible for second cancers as there were too few events).

Median overall survival was 1.99 years (95% CI 1.75-2.20). Not surprisingly, results for overall survival were similar to those of lung cancer survival, given that 86% of deaths were lung cancer-related (Models 1os-4os). There was an important interaction by treatment centre (Model 2os), with an improvement in survival with increasing intended EQD2T in Reading (HR 0.84, 95% CI 0.74-0.95) and possibly Oxford (HR 0.93, 95% CI 0.85-1.01), while there was a reduction in survival in Northampton with increasing intended EQD2T (HR 1.15, 95% CI 1.02-1.29).

Fewer than 50% of patients developed a second primary cancer of another site, so a median time to event could not be calculated. Given there were only 22 second cancers, models examining an association with intended EQD2T were underpowered (Models 1sc-3sc). However, one might expect an increase in second cancers among patients who received higher doses of radiotherapy,

Table 4.14: Overall survival and hazard of developing second cancers, intended EQD2T (N=324)

EQD2T (Gy)	Level of effect modification		No. events/ patients	HR	SE	95% CI	p_{Wald}*	p_{LR}‡ test comparing to simpler model
Model 1os: Overall survival, continuous dose*								
Trend per Gy			303/324	0.97	0.03	(0.92, 1.03)	0.3	-
Model 2os: Model 1 with effect modification by treatment centre*								Comparing to Model 1os
Trend per Gy	Oxford		141/148	0.93	0.04	(0.85, 1.01)	0.1	0.003
	Reading		60/66	0.84	0.05	(0.74, 0.95)	0.005	
	Northampton		70/75	1.15	0.07	(1.02, 1.29)	0.02	
	Leicester		32/35	0.97	0.11	(0.77, 1.22)	0.8	
Model 3os: Model 1 with effect modification by chemotherapy*								Comparing to Model 1os
Trend per Gy	No CT		183/193	0.92	0.04	(0.84, 1.00)	0.04	0.07
	Any CT		120/131	1.02	0.04	(0.94, 1.11)	0.6	
Model 4os: Model 1 with effect modification by both chemotherapy and centre*								Comparing to Model 1os
Trend per Gy	Oxford	No CT	91/93	0.94	0.07	(0.80, 1.09)	0.4	0.02
		Any CT	50/55	0.93	0.06	(0.83, 1.05)	0.3	
	Reading	No CT	34/38	0.82	0.08	(0.67, 1.00)	0.05	
		Any CT	26/28	0.87	0.07	(0.74, 1.03)	0.1	
	Northampton	No CT	28/29	0.98	0.11	(0.79, 1.21)	0.8	
		Any CT	42/46	1.19	0.09	(1.03, 1.37)	0.02	
	Leicester	No CT	30/33	0.96	0.12	(0.76, 1.22)	0.8	
		Any CT	2/2	0.94	0.07	(0.80, 1.09)	0.4	
Model 1sc: Hazard of developing second cancer, continuous dose§								
Trend per Gy			22/324	0.92	0.11	(0.73, 1.16)	0.5	-
Model 2sc: Model 5 with effect modification by treatment centre§								Comparing to Model 1sc
Trend per Gy	Oxford		10/148	0.92	0.19	(0.61, 1.39)	0.7	0.7
	Reading¦		1/66					
	Northampton		5/75	0.85	0.19	(0.56, 1.30)	0.5	
	Leicester		6/35	1.14	0.30	(0.68, 1.92)	0.6	
Model 3sc: Model 5 with effect modification by chemotherapy§								Comparing to Model 1sc
Trend per Gy	No CT		18/193	0.89	0.13	(0.67, 1.18)	0.4	0.6
	Any CT		4/131	1.00	0.21	(0.66, 1.50)	0.99	

* Wald test of association with outcome, separately for each category of variable, on one degree of freedom.

† Likelihood ratio test comparing more complex model with simpler model.

‡ Models were adjusted for chemotherapy yes/no, surgery, grouped age, sex, social deprivation trend, and trend across calendar

§ Models were adjusted for chemotherapy yes/no, grouped age, sex, social deprivation trend, and trend across calendar period. Adjustment by surgery not possible, because no patients who received surgery went on to develop a non-lung second cancer.

¦ Hazard ratio could not be estimated due to insufficient number of patients.

Abbreviations: HR=hazard ratio. SE=standard error. CI=confidence interval. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number

and the trend, while not statistically significant, indicated a reduction rather than an increase in hazard (HR 0.92, 95% CI 0.73-1.16, Model 1sc).

3.2.3.f Analysis by treatment centre

In a separate analysis of lung cancer survival by treatment centre, excluding radiotherapy dose as a co-variate, there was no association between lung cancer survival and treatment centre (p=0.9, Table 4.15).

Table 4.15: Lung cancer survival, by treatment centre (N=324)*

Treatment Centre	No. events/ patients	HR	SE	95% CI	p_{Wald} †	Joint p_{LR} ‡
Model: Treatment Centre as principal independent variable, with same covariates as in EQD2T models						
Oxford	120/148	1				0.9
Reading	55/66	0.95	0.16	(0.68, 1.34)	0.8	
Northampton	64/75	0.90	0.15	(0.65, 1.26)	0.6	
Leicester	23/35	0.89	0.21	(0.55, 1.43)	0.6	

* Model was adjusted for chemotherapy yes/no, surgery, grouped age, sex, social deprivation trend, and trend across calendar period

† Wald test of association with outcome, separately for each centre, on one degree of freedom.
‡ Joint likelihood ratio test of association with outcome, of all four centres, on three degrees of freedom.

Abbreviations: LC=lung cancer. HR=hazard ratio. SE=standard error. CI=confidence interval. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number

3.3 Invasive Breast Cancer

3.3.1 Descriptive analyses

Assumed radiotherapy fractionations based on numbers of fractions recorded in the CIA data are presented separately by treatment centre (Table 4.4). Standard numbers of fractions were 12, 13, 15, 18, 20, 23, 25, 28, and 30. Patients who received non-standard numbers of fractions are also shown, with an indication of the assumed intended fractionation for their non-standard number of fractions. Of the 8,879 eligible breast patients, 136 had a record of having received a non-standard number of radiotherapy fractions (numbers in blue and italics). As was the case with NSCLC, Reading had the highest proportion (6%) of patients with a record of non-standard fractions.

There was a high degree of variability in the fractionations given by treatment centre (Figure 4.8). Most patients in Oxford (1,989/3,125) received 41.6 Gy in 13 fractions (a third with a boost), while most patients in Reading (476/1,077) and Mount Vernon (1,163/1,224) received 40 Gy in 15 fractions (most with a boost). In Northampton the commonest fractionation was 45 Gy in 20 fractions (1,634/2,658, very few with a boost), and in Leicester it was 50 Gy in 25 fractions (533/795). Leicester had no record of giving any boosts, though it is unclear whether this is because of the way they recorded data or whether patients did indeed not receive boosts. In Northampton, very few patients had a record of a boost, while in Mount Vernon and Oxford, just under half of patients received a boost. 41.6 Gy in 13 fractions was only given to patients in Oxford and 40 Gy in 12 fractions only to patients in Reading. Overall, 21% of patients (1,859/8,879) received the international convention of 50 Gy in 25 with or without a boost.

Changes in fractionation over calendar period are also depicted (Figure 4.9). In 2004-05 the most common fractionations were 45 Gy in 20 and 41.6 Gy in 13, though by 2008-09 the most commonly given fractionation was 40 Gy in 15, and in 2010-11 no patients received 41.6 Gy in 13

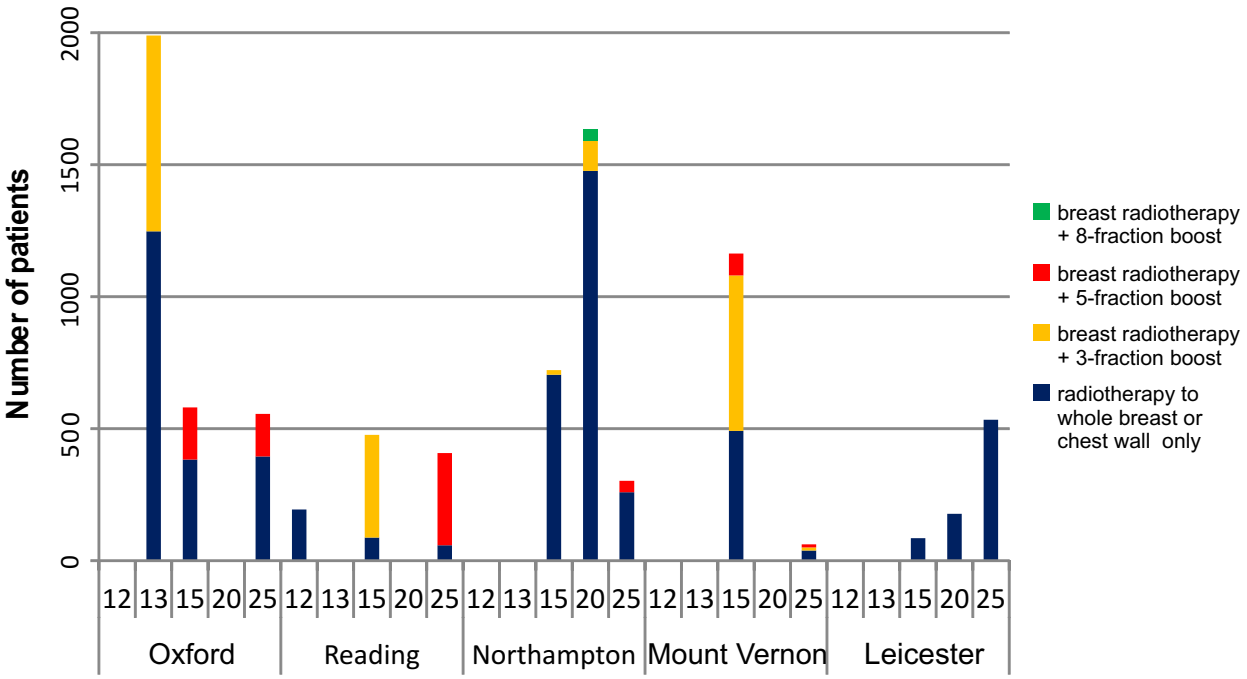
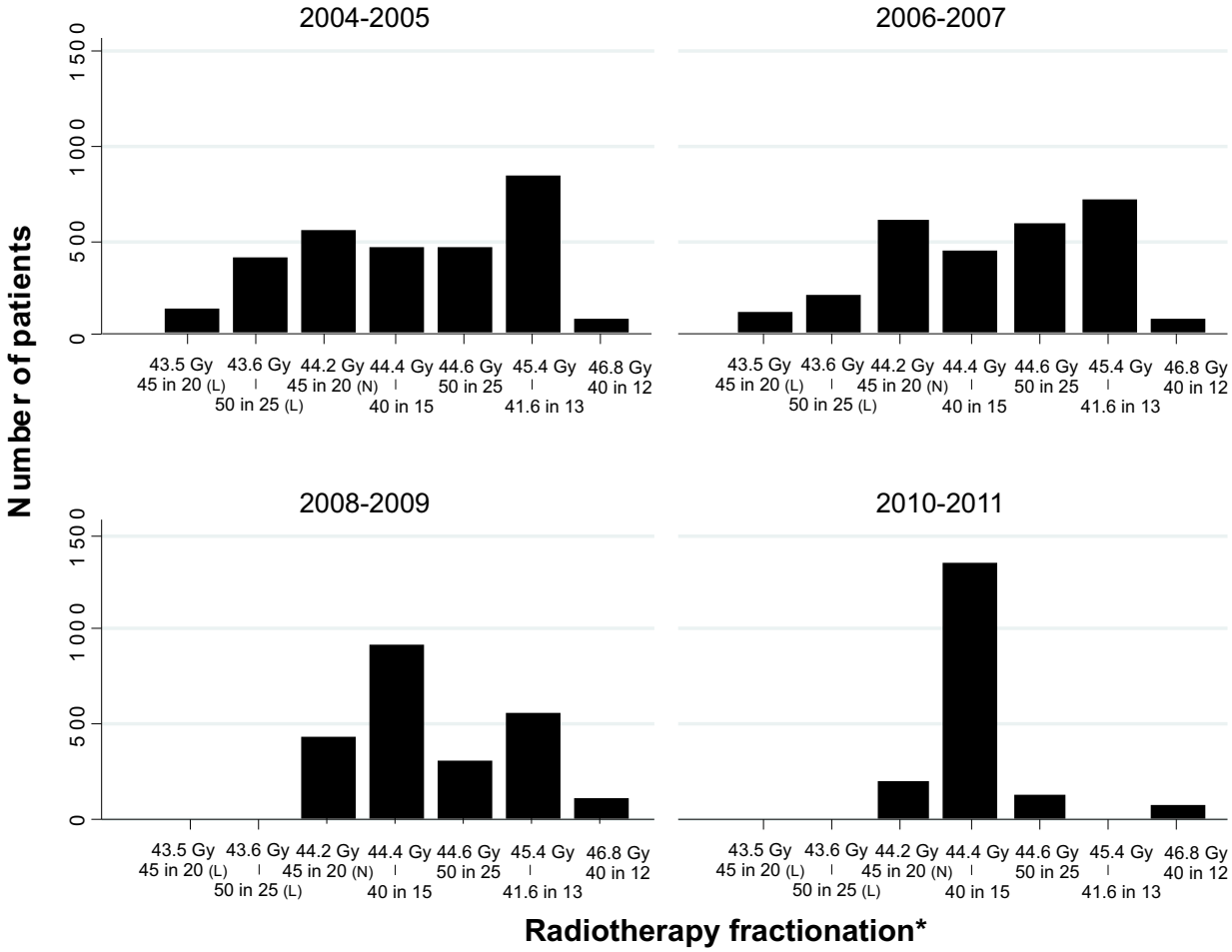


Figure 4.8: No. of breast cancer patients by radiotherapy fractions delivered to the whole breast or chest wall, for each centre



*L=Leicester only, N=Northampton only. Equivalent dose in 2 Gy fractions corrected for time (EQD2T) indicated in top line, total dose and number of fractions in bottom line.

Figure 4.9: Number of breast cancer patients treated by radiotherapy regimen, over calendar period.

and 83% of patients received 40 Gy in 15. The number of patients receiving 50 Gy in 25 remained stable between 2004 and 2007 at about 30%, but by 2010-11, this was reduced to 6% (Figure 4.9). The number of treatment days over which any given fractionation was reported as having been received ranged widely (Figure 4.10). For example, the minimum number of treatment days recorded for patients who received 40 Gy in 15 fractions was 1 and the maximum 168 (mean 22.3 days, standard deviation 7.1 days). The minimum number of treatment days recorded for patients who received 50 Gy in 25 fractions was also 1 and the maximum 118 (mean 36.8 days, standard deviation 5.2 days).

Intended EQD2T to the whole breast/chest wall ranged from 43.5 Gy (45 Gy in 20 in Leicester[10]) to 46.8 Gy (40 Gy in 12 fractions in Reading), with a mean of 44.6 Gy (Table 4.16). If the boost dose was added to the dose received to the whole breast/chest wall, intended EQD2T ranged from 43.5 Gy (Leicester) to 57.7 Gy (Mount Vernon), with a mean of 47.2 Gy. For the 7,549/8,879 patients included in analyses of actual EQD2T, the EQD2T including boost dose ranged from 41.6 Gy to 58.3 Gy, with a mean of 46.8 Gy. The mean actual dose for these 7,549 patients (46.8 Gy) was lower than the intended dose for all 8,879 patients (47.2 Gy), because more patients received treatment in a higher than a lower number of days, reducing the EQD2T.

By 31 December, 2016, 31% of patients had experienced a breast cancer event (recurrence, metastases, contralateral breast cancer or breast-cancer death)[11], 12% had died of breast cancer, and 7% had died of a cause other than breast cancer (Table 4.16). The mean follow-up time to a breast cancer event was 6.7 years (range of 0.3-12.8 years) and to any death was 8.6 years (range of 0.5-13.8 years, Table 4.16).

[10] For the 50 Gy in 25 and 45 Gy in 20 fractionations in Leicester, an intended three more days of treatment than at other centres was assumed, given the distribution of treatment days for most patients at that centre (Appendix 3, Supplementary Text 3). That is why the intended EQD2T for these two fractionations in Leicester is lower than elsewhere.

[11] A break-down of the type of breast cancer event first experienced by the women in this study is available in Table 4.17.

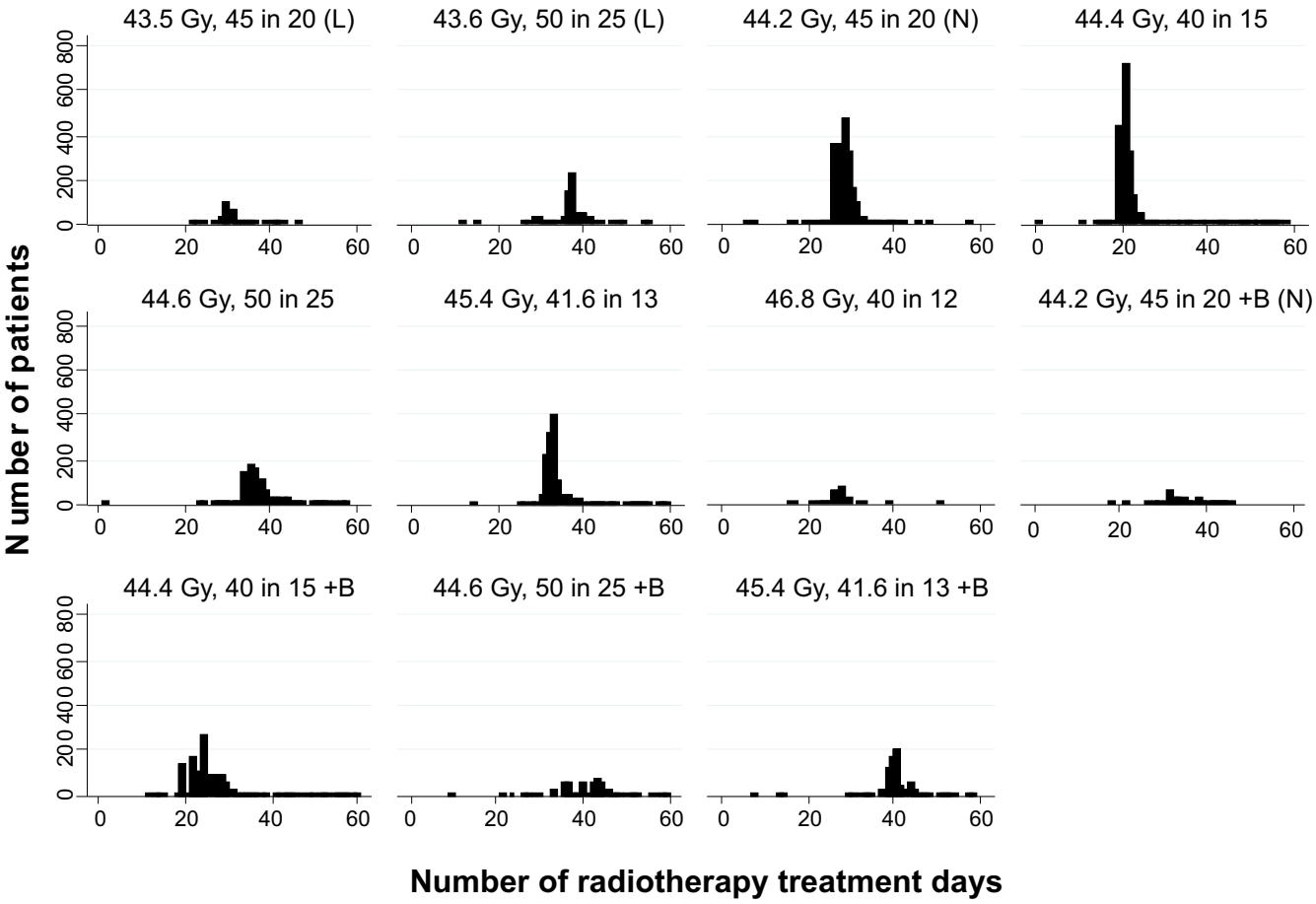


Figure 4.10: Number of breast cancer patients treated by no. of treatment days for each radiotherapy fractionation. L=Leicester only, N=Northampton only, +B=plus boost. Data for patients with more than 60 treatment days are not displayed.

Table 4.16: Descriptive characteristics of breast patient population

	Total no. patients	Breast event			BC death		Non BC death		Any death		Intended EQD2T
		Mean (SD)	%	p*	%	p*	%	p*	%	p*	p*
All patients	8,879		31		12		7		18		-
Follow-up time (years)											
Breast event		6.7 (3.4)									
Any death		8.6 (2.9)									
Intended EQD2T dose to whole breast/chest wall (Gy), Total dose (Gy) in no. fractions†											
43.5, 45 in 20 (L)	177	44.6 (0.6)	54	<0.001	28	<0.001	6	<0.001	34	<0.001	-
43.6, 50 in 25 (L)	533		23		10		7		17		
44.2, 45 in 20 (N)	1,634		35		13		8		21		
44.4, 40 in 15	3,026		28		9		5		14		
44.6, 50 in 25	1,326		36		13		4		17		
45.4, 41.6 in 13 (O)	1,989		28		12		9		21		
46.8, 40 in 12 (R)	194		41		18		7		25		
Radiotherapy boost											
None	6,126		32	<0.001	13	<0.001	7	0.06	20	<0.001	<0.001
Any	2,753		27		8		6		14		
Intended EQD2T dose including boost dose (Gy), Total dose (Gy) in no. fractions†											
43.5, 45 in 20 (L)	177	47.2 (4.2)	54	<0.001	28	<0.001	6	<0.001	34	<0.001	-
43.6, 50 in 25 (L)	533		23		10		7		17		
44.2, 45 in 20 (N)	1,476		36		13		8		22		
44.4, 40 in 15	1,750		28		10		5		15		
44.6, 50 in 25	749		42		16		3		19		
45.4, 41.6 in 13 (O)	1,247		28		13		10		23		
46.8, 40 in 12 (R)	194		41		18		7		25		
50.8, 41.6 in 13 (O)	742		29		11		7		18		
51.76, 50 in 25 (O, R, N)	323		25		6		3		9		
51.80, 40 in 15 (O)	197		27		5		2		7		
53.1, 45 in 20 (N)	114		23		6		3		9		
53.4, 40 in 15 (R,N)	407		31		4		3		8		
54.0, 40 in 15 (MV)	83		18		7		10		17		
54.6, 50 in 25 (R, MV)	131		27		11		6		18		
55.8, 45 in 20 (N)	44		27		7		11		18		
56.1, 40 in 15 (MV)	241		24		10		10		19		
57.6, 40 in 15 (MV)	348		28		8		6		14		
57.7, 50 in 25 (MV)	12		42		25		0		25		
Grouped actual EQD2T dose including boost dose (Gy), No. patients=7,549											
41.0-42.9	211	46.8 (4.2)	29	<0.001	12	<0.001	9	0.004	21	<0.001	-
43.0-43.9	1,470		35		14		7		21		
44.0-44.9	2,586		31		11		6		17		
45.0-45.9	1,057		31		14		8		22		
46.0-49.9	214		39		16		6		22		
50.0-51.9	849		27		8		6		14		
52.0-53.9	516		30		5		3		7		
54.0-55.9	193		23		10		6		16		
56.0-59.0	453		28		8		7		15		
Treatment Centre											
Oxford	3,125		30	0.02	12	0.01	6	0.07	18	<0.001	<0.001
Reading	1,077		30		9		5		14		
Northampton	2,658		33		12		7		19		
Mount Vernon	1,224		29		11		6		17		
Leicester	795		30		13		9		22		

Table continued on next page.

Table 4.16 continued

	Total no. patients	Breast event Mean (SD)	Breast event %	Breast event p*	BC death %	BC death p*	Non BC death %	Non BC death p*	Any death %	Any death p*	Intended EQD2T p*
Age (years)											
20-39	501	57.8 (11.6)	52	<0.001	20	<0.001	1	<0.001	21	<0.001	<0.001
40-49	1,686		38		12		1		13		
50-59	2,655		29		9		4		13		
60-69	2,650		26		10		7		17		
70-79	1,159		27		15		17		32		
80+	228		29		21		36		57		
Number of nodes involved											
0	4,807		23	<0.001	6	<0.001	6	0.06	13	<0.001	<0.001
1-3	1,932		38		14		6		20		
4 or more	825		61		35		6		41		
Unknown	1,315		29		13		8		21		
Cancer stage											
0-1A	2,388		20	<0.001	5	<0.001	7	<0.001	13	<0.001	<0.001
2-2B	2,424		40		17		8		25		
3-3A	419		51		28		8		36		
Unknown	3,648		30		10		5		15		
Morphology											
Ductal	6,945		32	<0.001	12	<0.001	6	0.8	18	<0.001	<0.001
Lobular	891		30		12		7		19		
Ductal and Lobular	309		31		13		7		20		
Tubular	295		12		2		5		7		
Mucinous	152		14		5		7		12		
Other/Unspecified	287		31		10		8		17		
Social deprivation (quintiles of IMD score)											
Least deprived	4,220		30	0.05	11	0.2	6	<0.001	17	<0.001	<0.001
2nd	2,121		31		11		6		17		
3rd	1,183		32		12		8		20		
4th	921		34		14		8		22		
Most deprived	434		33		13		10		24		
Calendar period											
2004-2005	2,658		32	<0.001	16	<0.001	10	<0.001	25	<0.001	<0.001
2006-2007	2,490		32		12		7		20		
2008-2009	2,131		32		9		5		13		
2010-2011	1,600		25		7		3		10		
Cytotoxic Chemotherapy											
No	5,891		23	<0.001	9	<0.001	8	<0.001	17	0.007	<0.001
Yes	2,988		47		17		3		20		
Surgery type											
BCS	6906		26	<0.001	8	<0.001	6	0.4	14	<0.001	<0.001
Mastectomy	1973		50		24		7		30		
Hormone therapy											
Unknown	7,119		32	<0.001	12	0.002	6	0.4	18	0.05	<0.001
Yes	1,760		26		9		7		16		
HER-2 treatment											
Unknown	8,704		30	<0.001	12	0.8	7	0.009	18	0.06	<0.001
Yes	175		77		11		2		13		

* Chi squared test of overall association.

† L=Leicester, N=Northampton, O=Oxford, R=Reading, MV=Mount Vernon

Abbreviations: SD=standard deviation. EQD2T=time-corrected equivalent dose in 2 Gy fractions. IMD=Indices of Multiple Deprivation.BCS=breast conserving surgery.

Table 4.17: Types of first breast event (N=8,879)

Breast event	No.	%
Death from breast cancer within three months of first registration	81	1
Confirmed distant metastases to liver/lung/bone/brain	421	5
Distant metastasis - other locations	86	1
Record of palliative care	5	0
Distant metastasis to liver/lung/bone/brain	525	6
Recurrence in ipsilateral regional lymph nodes	68	1
Recurrence in regional lymph nodes with no laterality recorded	113	1
Recurrence in ipsilateral breast	334	4
Recurrence, type unknown	835	9
Contralateral breast cancer	246	3
Microscopically confirmed primary cancer of liver/lung/brain/bone	50	1
Microscopically unconfirmed primary cancer of liver/lung/brain/bone	10	0
New primary non-breast cancer	302	3
Death from non-breast cancer	5	0
Death with no cause recorded in the registry	2	0
Death from cause other than cancer	240	3
Embarkation	8	0
None	5,548	62
TOTAL	**8,879**	**100**

Intended EQD2T to the whole breast/chest wall was strongly associated with all outcomes, even with non-breast-cancer death ($p<0.001$). This was true also of whether any radiotherapy boost had been received, and receipt of boost was also associated with intended EQD2T ($p<0.001$). Actual EQD2T was also strongly associated with all outcomes.

Treatment centre was associated strongly with death due to any cause ($p<0.001$). However, this is probably because the highest proportion of deaths was in Leicester (22%), where data were only available up to 2006. Patients who were diagnosed in earlier years were more likely to have died by the end of the study period. Treatment centre was also associated with having a breast cancer event ($p=0.02$), breast cancer death ($p=0.01$), and only weakly with non-breast-cancer death ($p=0.07$). It was strongly associated with intended EQD2T. This is not surprising given the large variation in fractionation between centres ($p<0.001$).

Most patients were diagnosed between the ages of 50 and 70, and the mean was 57.8 years. All outcomes and intended EQD2T were associated with age. The highest proportion of breast cancer events was seen in the youngest age group (52%). The proportion of non-breast-cancer deaths was highest in the oldest age groups.

The higher the number of nodes involved, the worse the breast cancer-related outcomes ($p<0.001$ for breast events and breast cancer death). Intended EQD2T differed highly significantly by number of nodes involved ($p<0.001$), suggesting that different fractionations were used depending on nodal status. Cancer stage was associated with all outcomes, though the association with non-breast-cancer death was driven by the unknown stage group. Stage was also associated strongly with intended EQD2T ($p<0.001$).

Morphology was available for all but 3% of patients (287/8,879 missing). Patients with tubular breast cancer were the least likely to develop a breast cancer event (12% of these women had a breast event), followed closely by those with mucinous cancers (14%). Those with ductal cancers were most likely to develop a breast cancer event (32%) and were also by far the most in number

(78%). Overall, morphology was associated strongly with breast-cancer related outcomes ($p<0.001$) but not with non-breast-cancer death ($p=0.8$). Morphology was also associated with intended EQD2T ($p<0.001$).

The more socially deprived patients were slightly more likely to develop a breast cancer event ($p=0.05$) but very much more likely to die of non-breast-cancer causes ($p<0.001$). Interestingly, social deprivation was associated with intended EQD2T ($p<0.001$).

Calendar period was associated with all outcomes ($p<0.001$). Most deaths were experienced by women diagnosed in the earliest years of the study, but this is a function of follow-up time. For women diagnosed more recently, the time from their diagnosis to the end of follow-up was less than for women diagnosed in earlier years. The same should be true also for the proportions of women with any breast event, by calendar period. There would be fewer breast events expected in later years. Fewer women indeed experienced breast events if they were diagnosed in 2010-11 compared to earlier years, but the difference in the proportions with breast events is not as big as expected given less follow-up time. Intended EQD2T was associated with calendar period, as also described above ($p<0.001$).

Use of cytotoxic chemotherapy was associated with developing a breast cancer event ($p<0.001$): 47% of patients given chemotherapy experienced an event versus 23% of patients not given chemotherapy. Patients not given chemotherapy were more likely to die of non-breast-cancer causes ($p<0.001$). Receiving chemotherapy was also associated with intended EQD2T ($p<0.001$).

Patients who underwent mastectomy were more likely to have a breast cancer event than women who had BCS ($p<0.001$), and they were three times more likely to die of breast cancer ($p<0.001$). Surgery type was not associated with non-breast-cancer death ($p=0.4$) but it was associated with intended EQD2T ($p<0.001$).

Hormone therapy and HER-2 treatment were not systematically reported in the cancer registration system, and information on these treatments was extracted from text fields. It is

therefore not possible to know whether patients without a record of these treatments received them. Nevertheless, 20% of women had a record of receiving hormone therapy and 2% of receiving HER-2 treatment. Those receiving hormone therapy were less likely to develop a breast cancer event than those with no record of treatment (<0.001). They were equally likely to die of non-breast-cancer causes (p=0.4). Those who received HER-2 treatment were much more likely to develop a breast cancer event (77% versus 30%, p<0.001), though they were equally likely to die of breast cancer (p=0.8) and less likely to die of non-breast-cancer causes (p=0.009). Both hormone and HER-2 treatment were associated with intended EQD2T (p<0.001).

3.3.2 Survival analyses

3.3.2.a Hazard of any breast cancer event and intended EQD2T dose

The principal analysis of interest in invasive BC was whether intended EQD2T to the whole breast/chest wall was associated with time to first breast cancer event. Fewer than 50% of patients experienced any event analysed in this study, so median times to event could not be calculated. In a Kaplan-Meier Plot, there was a strong association between intended EQD2T and having a breast cancer event (p<0.0001) and weak evidence of a trend of increasing breast cancer events with increasing intended EQD2T (p=0.05, Figure 4.11). Similarly this unadjusted association was seen in an unadjusted Cox regression, in which the overall association between intended EQD2T as a variable with seven categories and hazard of a first breast cancer event had a p-value of less than 0.0001 (Table 4.18).

A fully adjusted Cox regression model showed which co-variates were associated with a breast cancer event (Table 4.19). Hazard ratios compare each category of each variable to a baseline level of that variable. In addition to category-specific p-values, a joint likelihood ratio test determines the joint association of that variable with a breast cancer event. Where applicable, a p-value for linear trend is presented.

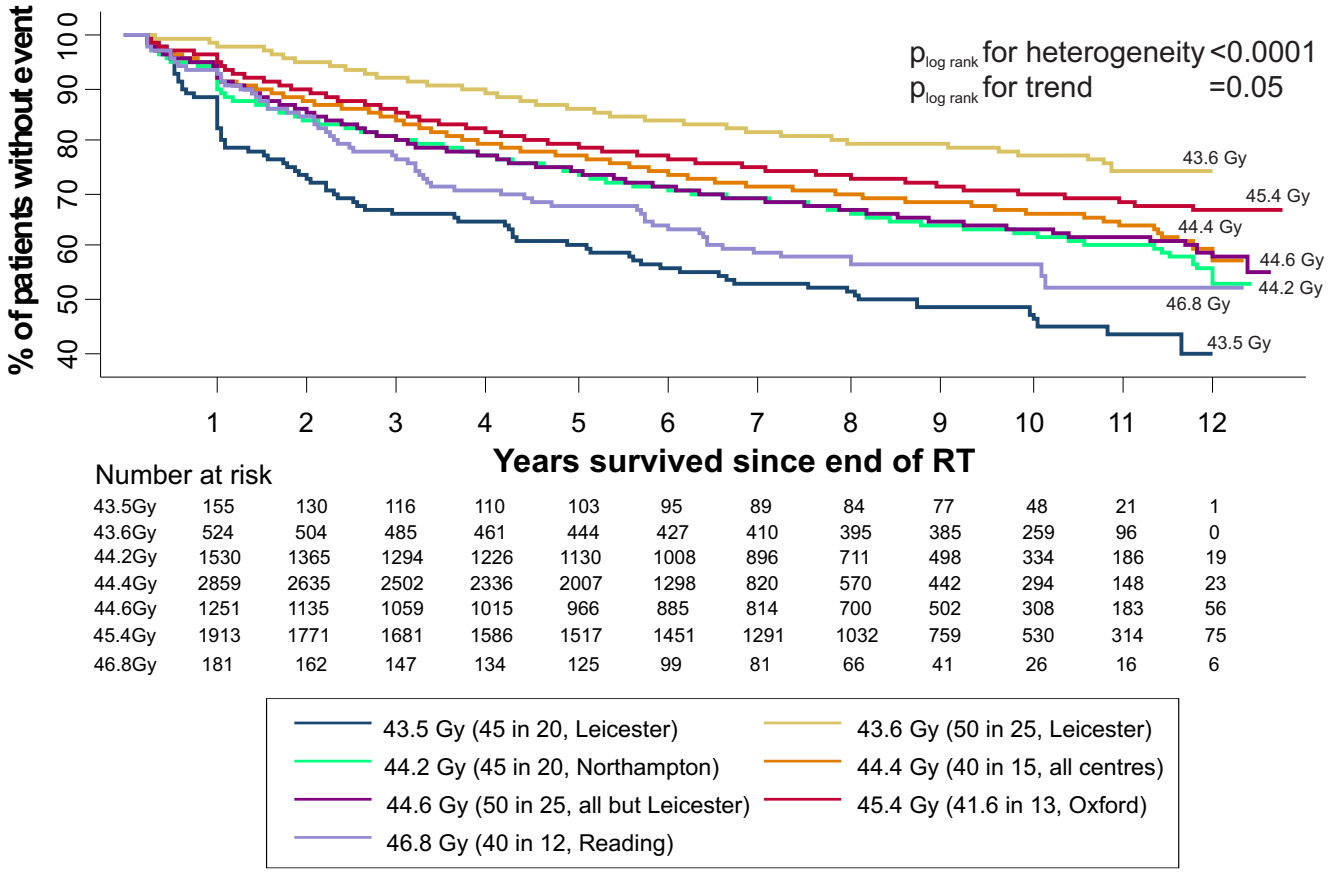


Figure 4.11: Time to breast-related event by intended EQD2T (N=8879)

Table 4.18: Hazard of BC event, unadjusted (N=8,879)

EQD2T (Gy)	Total dose (Gy) in no. fractions	Centre	No. events/ patients	HR	SE	95% CI	p_{Wald}*	Joint p_{LR}†
43.5	45 in 20	Leicester	95/177	1.92	0.21	(1.55, 2.37)	<0.0001	<0.0001
43.6	50 in 25	Leicester	122/533	0.62	0.06	(0.51, 0.75)	<0.0001	
44.2	45 in 20	Northampton	573/1,634	1.16	0.06	(1.04, 1.29)	0.007	
44.4	40 in 15	All	839/3,026	1				
44.6	50 in 25	All but Leicester	471/1,326	1.12	0.06	(1.00, 1.25)	0.06	
45.4	41.6 in 13	Oxford	563/1,989	0.86	0.05	(0.77, 0.95)	0.005	
46.8	40 in 12	Reading	80/194	1.46	0.17	(1.16, 1.84)	0.001	

* Wald test of association with outcome, separately for each category of EQD2T, on one degree of freedom.

† Joint likelihood ratio test of association with outcome, of EQD2T variable including all seven categories, on six degrees of freedom.

Abbreviations: BC=breast cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number.

Table 4.19: Hazard of BC event, adjusted for all available factors and indicating degree of confounding by each factor (N=8,879)

			No. events/ patients	HR	SE	95% CI	p_{Wald}*	Joint p_{LR}†	p_{Wald} trend§	Degree of confounding§
EQD2T (Gy)	**Total dose (Gy) in no. fractions**	**Centre**								
43.5	45 in 20	Leicester	95/177	1.26	0.19	(0.93, 1.69)	0.1	<0.0001	<0.0001	-
43.6	50 in 25	Leicester	122/533	0.76	0.10	(0.58, 0.98)	0.03			
44.2	45 in 20	Northampton	573/1,634	1.09	0.07	(0.97, 1.24)	0.1			
44.4	40 in 15	All	839/3,026	1						
44.6	50 in 25	All but Leicester	471/1,326	0.92	0.06	(0.81, 1.04)	0.2			
45.4	41.6 in 13	Oxford	563/1,989	0.84	0.05	(0.74, 0.95)	0.005			
46.8	40 in 12	Reading	80/194	0.78	0.10	(0.61, 0.99)	0.04			
Boost to tumour bed										None
No			1,987/6,126	1				-	-	
Yes			756/2,753	0.96	0.05	(0.86, 1.07)	0.5			
Age (years)										Very slight
20-40			260/501	1.55	0.11	(1.34, 1.79)	<0.0001	<0.0001	-	
40-50			641/1,686	1.09	0.06	(0.98, 1.22)	0.1			
50-60			769/2,655	1						
60-70			689/2,650	1.02	0.05	(0.92, 1.13)	0.7			
70-80			317/1,159	1.07	0.08	(0.93, 1.23)	0.3			
80+			67/228	1.45	0.19	(1.12, 1.88)	0.005			
Number of nodes involved										Major
0			1,123/4,807	1				<0.0001	<0.0001	
1-3			729/1,932	1.15	0.06	(1.04, 1.28)	0.009			
4 or more			506/825	1.84	0.12	(1.62, 2.08)	<0.0001			
Unknown			385/1,315	1.15	0.10	(0.97, 1.36)	0.1			
Cancer stage										Slight
0-1A			470/2,388	1				<0.0001	<0.0001	
2-2B			977/2,424	1.36	0.09	(1.20, 1.54)	<0.0001			
3-3A			213/419	1.57	0.16	(1.28, 1.91)	<0.0001			
Unknown			1083/3,648	1.29	0.09	(1.12, 1.48)	<0.0001			
Morphology										Very slight
Ductal			2,229/6,945	1				<0.0001	-	
Lobular			271/891	0.80	0.05	(0.71, 0.92)	0.001			
Ductal and Lobular			97/309	0.92	0.10	(0.75, 1.13)	0.4			
Tubular			36/295	0.53	0.09	(0.38, 0.74)	<0.0001			
Mucinous			22/152	0.57	0.12	(0.38, 0.88)	0.01			
Other/Unspecified			88/287	1.04	0.11	(0.84, 1.29)	0.7			
Social deprivation (quintiles of IMD score)										None
Least deprived			1,248/4,220	1				0.5	0.1	
2nd			659/2,121	1.05	0.05	(0.95, 1.15)	0.4			
3rd			380/1,183	1.07	0.06	(0.96, 1.21)	0.2			
4th			314/921	1.11	0.07	(0.98, 1.26)	0.1			
Most deprived			142/434	1.05	0.09	(0.88, 1.25)	0.6			
Calendar period										None¶
2004-2005			861/2,658	1				0.02	0.02	
2006-2007			797/2,490	1.12	0.06	(1.01, 1.24)	0.03			
2008-2009			680/2,131	1.18	0.08	(1.04, 1.34)	0.009			
2010-2011			405/1,600	1.06	0.09	(0.89, 1.25)	0.5			

Table continued on next page.

Table 4.19 continued

	No. events/ No. patients	HR	SE	95% CI	p_{Wald}*	Joint p_{LR}†	p_{Wald} trend‡	Degree of confounding§
Cytotoxic Chemotherapy								Very slight
No	1,326/5,891	1				-	-	
Yes	1,417/2,988	1.69	0.08	(1.54, 1.86)	<0.0001			
Surgery type								Major
BCS	1,761/6,906	1				-	-	
Mastectomy	982/1,973	1.39	0.08	(1.24, 1.55)	<0.0001			
Hormone therapy								None
Unknown	2,288/7,119	1				-	-	
Yes	455/1,760	0.91	0.05	(0.82, 1.01)	0.08			
HER-2 treatment								Slight
Unknown	2,609/8,704	1				-	-	
Yes	134/175	3.40	0.33	(2.82, 4.11)	<0.0001			

* Wald test of association with outcome, separately for each category of variable, on one degree of freedom.
† Joint likelihood ratio test of association with outcome, of variable including all *n* categories, on (*n* -1) degrees of freedom.
‡ Wald test for linear trend across variable.
§ Degree of confounding was assessed by examining this full model with a model excluding each of the potential confounders, one by one. See Methods for detailed explanation.
¦ Test excludes patients missing information on this variable

¶ Calendar period is retained as a covariate in subsequent models, as it is a confounder of breast-specific and overall survival

Abbreviations: BC=breast cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number. IMD=indices of multiple deprivation. BCS=breast conserving surgery. HER-2=human epidermal growth factor receptor 2.

In this fully adjusted model, intended EDQ2T was strongly associated with hazard of a breast cancer event (p<0.0001, Table 4.19). Using the most common regimen (40 Gy in 15) as a baseline, the group in the lowest dose category (45 Gy in 20 in Leicester) did worst (HR 1.26, 95% CI 0.93-1.69, p=0.1), while the group that did best was the next-lowest dose group (50 Gy in 25 in Leicester, HR 0.76, 95% CI 0.58-0.98, p=0.03). Age, number of nodes involved, stage, morphology, chemotherapy, surgery type, and HER-2 treatment were also strongly associated with developing a breast cancer event (all p<0.0001). Calendar period was somewhat associated (p=0.02) and hormone therapy weakly associated (p=0.08). Social deprivation and radiotherapy boost were not associated (both p=0.5).

In the fully adjusted model confounding of each co-variate varied (Table 4.19). The factors showing the highest degree of confounding were the number of nodes involved and surgery type. Stage, age, morphology, receipt of chemotherapy, and HER-2 treatment were only slight confounders. Neither receipt of radiotherapy boost nor of hormone therapy showed any confounding, nor did social deprivation or calendar period. Factors showing any degree of confounding were retained in the model as well as calendar period. Calendar period was found to be associated with other outcomes, and retaining this variable in the model permitted comparability between models with different outcomes.

A series of models of continuous intended EQD2T including relevant confounders fitted, with and without effect modifiers (Table 4.20), showed that the hazard of developing a breast cancer event decreased with increasing intended EQD2T to the whole breast/chest wall (HR 0.88, 95% CI 0.83-0.94, p<0.0001, Model 1). Adding in effect modification by surgery type (p for interaction=0.02, Model 2) clarified that women who had a mastectomy had a decrease in hazard of a breast cancer event with increasing dose (HR 0.83, 95% CI 0.76-0.90, p<0.0001) but this was not so for women who had BCS (HR 0.96, 95% CI 0.88-1.06, p=0.4). There was only weak evidence of an effect modification by surgery and boost (p=0.09, Model 3).

Table 4.20: Hazard of BC event, continuous intended radiotherapy dose, and effect modifiers (N=8,879)*

EQD2T (Gy)	Effect modifiers		No. events/ patients	HR	SE	95% CI	p_{Wald} †	p_{LR} ‡ test comparing this model to Model 1
Model 1: Continuous model for dose								
Trend per Gy			2,743/8,879	0.88	0.03	(0.83, 0.94)	<0.0001	-
Model 2: Continuous dose, effect modification by type of surgery								
Trend per Gy	BCS		1,761/6,906	0.96	0.05	(0.88, 1.06)	0.4	0.02
	Mastectomy		982/1,973	0.83	0.04	(0.76, 0.90)	<0.0001	
Model 3: Continuous dose, effect modification by type of surgery and receipt of boost								
Trend per Gy	BCS, no boost		1,005/4,153	0.94	0.05	(0.84, 1.05)	0.3	0.09
	Mastectomy		982/1,973	0.83	0.04	(0.76, 0.90)	<0.0001	
	BCS, boost		756/2,753	1.01	0.08	(0.86, 1.19)	0.9	
Model 4: Continuous dose, effect modification by type of surgery and centre								
Trend per Gy	Oxford	BCS	595/2,415	1.07	0.10	(0.88, 1.29)	0.5	0.009
		Mastectomy	343/710	0.80	0.10	(0.63, 1.01)	0.07	
	Reading	BCS	240/878	1.35	0.17	(1.06, 1.73)	0.02	
		Mastectomy	81/199	0.92	0.12	(0.72, 1.19)	0.5	
	Northampton	BCS	520/1,973	0.53	0.18	(0.27, 1.03)	0.06	
		Mastectomy	368/685	0.90	0.43	(0.35, 2.30)	0.8	
	Mount Vernon§	BCS	245/986	-				
		Mastectomy	116/238	-				
	Leicester	BCS	161/654	0.85	0.28	(0.45, 1.62)	0.6	
		Mastectomy	74/141	0.84	0.65	(0.18, 3.82)	0.8	

* All models adjusted for chemotherapy, surgery, grouped age, number of nodes involved, stage, morphology, HER 2 treatment, and continuous calendar period in years.

† Wald test of association with outcome, separately for each category of variable, on one degree of freedom.

‡ Likelihood ratio test comparing more complex model with simpler model.

§ Hazard ratio could not be estimated due to too narrow a range in EQD2T at Mount Vernon (44.44Gy-44.56Gy)

Abbreviations: BC=breast cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number. IMD=indices of multiple deprivation. BCS=breast conserving surgery. HER-2=human epidermal growth factor receptor 2.

The most significant effect modification was by surgery and centre (p=0.009, Model 4). In this model, in Oxford, there was no evident trend in dose among BCS patients (HR 1.07, 95% CI 0.88-1.29, p=0.5), while for mastectomy patients, the hazard ratio was 0.80 (95% CI 0.63-1.01, p=0.07). In Reading, hazard of a breast cancer event increased with increasing dose for BCS patients (HR 1.35, 95% 1.06-1.73, p=0.02), while there was no evident trend among mastectomy patients (HR 0.92, 95% CI 0.72-1.19, p=0.5). In Northampton, the apparent protective effect of higher dose among BCS patients was greatest (HR 0.53, 95% CI 0.27-1.03, p=0.6), but among mastectomy patients, there was no effect of dose (HR 0.90, 95% CI 0.35-2.30, p=0.8). Results for Leicester were not statistically significant, but the estimated hazard ratios for BCS and mastectomy patients were similar (BCS: HR 0.85, 95% CI 0.45-1.62, p=0.6; mastectomy: HR 0.84, 95% CI 0.18-3.82, p=0.8). Estimates could not be made for Mount Vernon, as patients only received either 44.44 Gy or 44.46 Gy to the whole breast/chest wall and as these are so similar in value, a trend per Gray could not be reliably assessed.

Statistically speaking, the better fit to the data was with intended EQD2T as a categorical rather than continuous variable (p testing for linearity of dose=0.001, Table 4.21, Model 5). If there were a perfect trend with increasing dose, one would expect all the hazards for lower doses than the baseline to be higher, while hazards for higher doses than the baseline should be lower. This was true, except for Leicester patients treated with 50 Gy in 25, who had a lower hazard of a breast cancer event than patients treated with the baseline fractionation, 40 Gy in 15 (HR 0.78, 95% CI 0.61-1.00, p=0.05). Further heterogeneity was evident in Model 6, with an interaction between dose and type of surgery (p=0.0003). Here, individual fractionations were more significantly associated with any breast cancer event than they were in simpler models. Especially among BCS patients there was no evident trend across increasing dose, though individual hazard ratios for some dose groups were statistically significant. Indeed those patients doing worst were those in the lowest and highest dose groups (Lowest: 45 Gy in 20 in Leicester compared to 40 Gy in 15 HR 2.49, 95% CI 1.59-3.92; Highest: 40 Gy in 12 in Reading compared to 40 Gy in 15 HR 2.11, 95% CI

Table 4.21: Hazard of BC event, categorical intended radiotherapy dose, and effect modifiers (N=8,879)*

EQD2T (Gy), Total dose (Gy) in no. fractions§	No. events/ patients	HR	SE	95% CI	p_{Wald} †	p_{LR} ‡ test comparing this to simpler model
Model 5: Categorical model for dose						Comparing categorical with continuous dose¦
43.5, 45 in 20 (L)	95/177	1.26	0.19	(0.94, 1.69)	0.1	0.001
43.6, 50 in 25 (L)	122/533	0.78	0.10	(0.61, 1.00)	0.05	
44.2, 45 in 20 (N)	573/1,634	1.17	0.07	(1.04, 1.31)	0.007	
44.4, 40 in 15	839/3,026	**1**				
44.6, 50 in 25	471/1,326	0.98	0.06	(0.86, 1.10)	0.7	
45.4, 41.6 in 13 (O)	563/1,989	0.90	0.05	(0.80, 1.01)	0.07	
46.8, 40 in 12 (R)	80/194	0.80	0.10	(0.63, 1.02)	0.07	
Model 6: Categorical model for dose, by type of surgery						Comparing to Model 5
Patients with BCS						
43.5, 45 in 20 (L)	23/43	2.49	0.58	(1.59, 3.92)	<0.0001	0.0003
43.6, 50 in 25 (L)	122/531	0.81	0.10	(0.63, 1.04)	0.10	
44.2, 45 in 20 (N)	333/1,209	1.20	0.09	(1.04, 1.38)	0.01	
44.4, 40 in 15	579/2,480	**1**				
44.6, 50 in 25	286/994	0.99	0.08	(0.85, 1.16)	0.9	
45.4, 41.6 in 13 (O)	405/1,627	0.96	0.07	(0.84, 1.10)	0.6	
46.8, 40 in 12 (R)	13/22	2.11	0.60	(1.21, 3.67)	0.008	
Patients with mastectomy						
43.5/43.6, 45 in 20/ 50 in 25 (L)	72/136	1.53	0.25	(1.11, 2.11)	0.009	
44.2, 45 in 20 (N)	240/425	1.77	0.15	(1.50, 2.09)	<0.0001	
44.4, 40 in 15	260/546	1.63	0.13	(1.40, 1.90)	<0.0001	
44.6, 50 in 25	185/332	1.53	0.14	(1.27, 1.83)	<0.0001	
45.4, 41.6 in 13 (O)	158/362	1.23	0.12	(1.02, 1.49)	0.03	
46.8, 40 in 12 (R)	67/172	1.07	0.14	(0.83, 1.39)	0.6	

* All models adjusted for chemotherapy, surgery, grouped age, number of nodes involved, stage, morphology, HER 2 treatment, and continuous calendar period in years .

† Wald test of association with outcome, separately for each category of variable, on one degree of freedom.

‡ Likelihood ratio test comparing more complex model with simpler model.

§ L=Leicester, N=Northampton, O=Oxford, R=Reading, MV=Mount Vernon

¦ Comparing this model with Table 4.20, Model 1

Abbreviations: BC=breast cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number. IMD=indices of multiple deprivation. BCS=breast conserving surgery. HER-2=human epidermal growth factor receptor 2.

1.21-3.67). There was no dose group among BCS patients that did significantly better than 40 Gy in 15.

Layering on a further effect modification by boost and by boost and centre was also statistically significant (p comparing to Model 5 in Table 4.21 <0.0001, for details see Appendix 3, Tables 1 and 2).

These categorical dose models are difficult to interpret, and it is more difficult to compare different models than if dose is continuous because there are many more numbers to compare. Also, using the continuous form of dose permits assessing any linear trend in increasing dose. For other measures of dose and other outcomes, models were therefore presented using continuous rather than categorical dose.

3.3.2.b Hazard of a breast cancer event: sensitivity analyses

Sensitivity analyses were conducted for the main outcome of interest, hazard of a breast cancer event, using continuous EQD2T and including an effect modification by type of surgery (Table 4.22). In a model including breast boost dose in the intended EQD2T calculation (Model 1), results were similar to the analogous model with just dose to the whole breast/chest wall (compare Table 4.20, Model 2). There was no trend with increasing intended EQD2T among BCS patients (HR 1.00, 95% CI 0.99-1.01, p=0.8), while for mastectomy patients the higher the dose the less hazard of a breast cancer event (HR 0.83, 95% CI 0.76-0.91, p<0.0001). Restricting this same analysis to only those included in the actual EQD2T analyses, the results were almost identical (Model 2 versus Model 1). In the actual EQD2T model (Model 3), results for BCS patients remained unchanged compared to Model 2 but results for mastectomy patients were attenuated (mastectomy: HR 0.92, 95% CI 0.85-0.99, p=0.03).

In an additional sensitivity analysis, events were censored for patients at age 75 in an analysis of intended EQD2T to the whole breast/chest wall (Model 4, Table 4.22). This analysis was performed in order to assess whether possible over-diagnosis of death due to breast cancer

Table 4.22: Hazard of breast cancer event: sensitivity analyses by type of surgery*

EQD2T (Gy)	Effect modifiers		No. events/ patients	HR	SE	95% CI	p_{Wald} †	p_{LR} ‡ test comparing to simpler model
	Type of surgery	Positive lymph nodes						
Panel A: Other forms of radiotherapy dose								
Model 1: Continuous intended dose including boost (N=8,768)								
Trend per Gy	BCS		1,731/6,795	1.00	0.01	(0.99, 1.01)	0.8	
	Mastectomy		982/1,973	0.83	0.04	(0.76, 0.91)	<0.0001	
Model 2: Model 1, including only patients in the actual EQD2T analysis (N=7,549)								
Trend per Gy	BCS		1,480/5,820	1.00	0.01	(0.99, 1.01)	0.9	
	Mastectomy		861/1,729	0.83	0.04	(0.76, 0.92)	<0.0001	
Model 3: Continuous actual dose including boost (N=7,549)								
Trend per Gy	BCS		1,480/5,820	1.00	0.01	(0.99, 1.01)	0.9	
	Mastectomy		861/1,729	0.92	0.04	(0.85, 0.99)	0.03	
Panel B: Events censored at age 75								
Model 4: Continuous intended dose (N=8,879)								
Trend per Gy	BCS		1,731/6,906	0.95	0.05	(0.87, 1.05)	0.3	
	Mastectomy		967/1,973	0.83	0.04	(0.76, 0.90)	<0.0001	
Panel C: Interaction by presence of positive nodes								Comparing to Model 2, Table 4.20
Model 5: Continuous intended dose, by presence of positive nodes (N=7,564)								
Trend per Gy	BCS	None	923/4,272	0.90	0.06	(0.78, 1.03)	0.1	0.9
		Any	538/1,431	0.95	0.08	(0.80, 1.13)	0.6	
	Mastectomy	None	181/465	0.76	0.08	(0.63, 0.93)	0.006	
		Any	688/1,295	0.81	0.05	(0.72, 0.90)	<0.0001	

* All models adjusted for chemotherapy, surgery, grouped age, number of nodes involved, stage, morphology, HER 2 treatment, and continuous calendar period in years.

† Wald test of association with outcome, separately for each category of variable, on one degree of freedom.

‡ Likelihood ratio test comparing more complex model with simpler model.

Abbreviations: BC=breast cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number. IMD=indices of multiple deprivation. BCS=breast conserving surgery. HER-2=human epidermal growth factor receptor 2.

among older patients may have driven results of analyses including events for all patients. Results were similar to those in which events were not censored (compare Model 2, Table 4.20). There was no significant trend among BCS patients (HR 0.95, 95% CI 0.87-1.05, p=0.3) while among mastectomy patients the higher the dose, the less hazard of a breast cancer event (HR 0.83, 95% CI 0.76-0.90, p<0.0001).

In a final sensitivity analysis, interaction between EQD2T and presence of any positive lymph nodes was assessed (Model 5, Table 4.22). Results were similar within type of surgery group, regardless of whether there was any detectable disease in lymph nodes. A likelihood ratio test was not significant, comparing this model with a model not including the interaction by presence of positive lymph nodes (comparing to Model 2, Table 4.20, p=0.9).

3.3.2.c Other outcomes: breast cancer-specific, overall, and non-breast-cancer survival

In addition to hazard of a breast cancer event, associations were examined between increasing intended EQD2T dose and (1) breast cancer survival, (2) overall survival and (3) non-breast-cancer survival. In the first two analyses, continuous intended EQD2T was used and an effect modification by type of surgery included. Co-variates included in these two models were the same as in the models with any breast cancer event as outcome.

In a model with just breast-cancer death as the outcome (Table 4.23), neither the trend with increasing intended EQD2T among BCS patients nor among mastectomy patients was significant, so an increase in dose was not associated with breast cancer survival (p=0.4 and p=0.3, respectively). The estimate of the hazard with increasing dose among BCS patients showed an increase rather than a decrease in hazard, opposite to the trend in hazard of a breast cancer event among BCS patients (BCS: HR 1.07, 95% CI 0.91-1.24; mastectomy: HR 0.93, 95% CI 0.82-1.06, compare Model 2, Table 4.20). All factors other than HER-2 treatment (age, number of nodes, stage, morphology, calendar year, chemotherapy, and surgery) were strongly associated with breast-cancer survival (all p<0.0001).

Table 4.23: Breast cancer survival, continuous intended EQD2T (N=8,879)

	Effect modifier	No. events/ patients	HR	SE	95% CI	p_{Wald}*	Joint p_{LR}†	p_{Wald}‡ trend
Continuous intended EQD2T, excluding boost information								
EQD2T trend per Gy	BCS	559/6,906	1.07	0.08	(0.91, 1.24)	0.4	-	-
	Mastectomy	464/1,973	0.93	0.06	(0.82, 1.06)	0.3	-	-
Age (years)								
20-40		101/501	1.58	0.19	(1.25, 2.00)	<0.0001	<0.0001	-
40-50		199/1,686	1.03	0.10	(0.85, 1.25)	0.7		
50-60		242/2,655	1					
60-70		259/2,650	1.34	0.12	(1.12, 1.60)	0.001		
70-80		173/1,159	1.84	0.20	(1.49, 2.27)	<0.0001		
80+		49/228	3.56	0.58	(2.58, 4.90)	<0.0001		
Number of nodes involved								
0		307/4,807	1				<0.0001	<0.0001§
1-3		261/1,932	1.31	0.12	(1.09, 1.58)	0.004		
4 or more		289/825	3.18	0.32	(2.62, 3.86)	<0.0001		
Unknown		166/1,315	1.38	0.16	(1.10, 1.74)	0.005		
Cancer stage								
0-1A		128/2,388	1				<0.0001	<0.0001§
2-2B		420/2,424	1.70	0.20	(1.35, 2.13)	<0.0001		
3-3A		117/419	2.19	0.33	(1.64, 2.94)	<0.0001		
Unknown		358/3,648	1.74	0.21	(1.37, 2.21)	<0.0001		
Morphology								
Ductal		838/6,945	1				<0.0001	-
Lobular		104/891	0.73	0.08	(0.59, 0.90)	0.003		
Ductal and Lobular		40/309	0.93	0.15	(0.68, 1.28)	0.7		
Tubular		5/295	0.24	0.11	(0.10, 0.58)	0.001		
Mucinous		8/152	0.52	0.18	(0.26, 1.04)	0.07		
Other/Unspecified		28/287	0.92	0.18	(0.63, 1.35)	0.7		
Trend across calendar period (2004-2011)								
Change per year		1,023/8,879	0.91	0.02	(0.87, 0.95)	<0.0001	-	-
Cytotoxic Chemotherapy								
No		526/5,891	1				-	-
Yes		497/2,988	1.33	0.10	(1.14, 1.55)	<0.0001		
Surgery type, effect calculated at mean EQD2T (44.63Gy)								
BCS		559/6,906	1				-	-
Mastectomy		464/1,973	1.72	0.13	(1.49, 1.99)	<0.0001		
HER-2 treatment								
Unknown		1,004/8.704	1				-	-
Any		19/175	0.82	0.20	(0.52, 1.31)	0.4		

* Wald test of association with outcome, separately for each category of variable, on one degree of freedom.
† Joint likelihood ratio test of association with outcome, of variable including all *n* categories, on (*n* -1) degrees of freedom.
‡ Wald test for linear trend across variable.
§ Test excludes patients missing information on this variable

Abbreviations: BC=breast cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number. IMD=indices of multiple deprivation. BCS=breast conserving surgery. HER-2=human epidermal growth factor receptor 2.

A higher number of nodes involved and more advanced cancer stage were even stronger predictors of breast cancer death than of any breast cancer event (compare Table 4.19). Unlike in the model of any breast cancer event, hazard of breast cancer death improved over calendar period, with a 9% decrease in hazard per year between 2004 and 2011 (HR 0.91, 95% CI 0.87-0.95, p<0.0001, Table 4.23). Unlike in the model for any breast cancer event, HER-2 treatment was not an independent factor for breast cancer death.

Unsurprisingly, given that two thirds of all deaths were due to breast cancer, results for overall survival were very similar to those for breast-cancer survival (Appendix 3, Table 3).

Associations between and confounding by co-variates and *non*-breast-cancer survival differed greatly from breast cancer survival (details in Appendix 3, Table 4). In particular, social deprivation was strongly associated with non-breast-cancer death and confounded the association with intended EQD2T. Three models of non-breast-cancer death were produced (Table 4.24). The first two, in which intended EQD2T is included as a categorical variable, illustrate that the hazard ratios for non-breast-cancer survival varied substantially with dose.

The first model includes the same co-variates as for the main analysis (hazard of a breast cancer event). The joint association of intended EQD2T and non-breast-cancer survival was highly significant (p=0.005, Model 1). Compared to 40 Gy in 15 fractions, the fractionations most strongly associated with non-breast-cancer death were 50 Gy in 25 in Leicester (HR 0.57, 95% CI 0.37-0.87, p=0.01) and 45 Gy in 20 in Northampton (HR 1.31, 95% CI 1.02-1.68, p=0.03).

The second model includes co-variates deemed to be confounders specifically of non-breast-cancer survival, in particular social deprivation. With these new covariates, intended EQD2T was no longer as strongly associated with non-breast-cancer survival (p=0.01, Model 2). However, estimates of the hazard ratios for individual fractionations are not very different to those in Model 1.

Table 4.24: Non breast cancer survival, intended radiotherapy dose (N=8,879)

EQD2T (Gy)	Total dose (Gy) in no.	Centre	No. events/ patients	HR	SE	95% CI	p_{Wald}*	Joint p_{LR}†	p_{Wald}‡ trend
Model 1: Categorical dose, adjusted for same factors as BC event analyses§									
	Total dose (Gy) in no.	**Centre**							
43.5	45 in 20	Leicester	11/177	0.65	0.24	(0.31, 1.36)	0.3	0.005	0.9
43.6	50 in 25	Leicester	39/533	0.57	0.13	(0.37, 0.87)	0.01		
44.2	45 in 20	Northampton	131/1,634	1.31	0.17	(1.02, 1.68)	0.03		
44.4	40 in 15	All	159/3,026	1					
44.6	50 in 25	All but Leicester	52/1,426	0.82	0.14	(0.59, 1.13)	0.2		
45.4	41.6 in 13	Oxford	172/1,989	1.04	0.12	(0.82, 1.31)	0.8		
46.8	40 in 12	Reading	14/194	0.93	0.27	(0.52, 1.66)	0.8		
Model 2: Categorical dose, adjusted for factors deemed to be confounders of Non-BC survival (Appendix 3, Table 4)¦									
	Total dose (Gy) in no.	**Centre**							
43.5	45 in 20	Leicester	11/177	0.67	0.22	(0.35, 1.29)	0.2	0.01	0.3
43.6	50 in 25	Leicester	39/533	0.54	0.12	(0.35, 0.82)	0.004		
44.2	45 in 20	Northampton	131/1,634	1.21	0.16	(0.94, 1.56)	0.1		
44.4	40 in 15	All	159/3,026	1					
44.6	50 in 25	All but Leicester	52/1,426	0.84	0.14	(0.61, 1.16)	0.3		
45.4	41.6 in 13	Oxford	172/1,989	1.07	0.13	(0.85, 1.35)	0.6		
46.8	40 in 12	Reading	14/194	1.06	0.30	(0.61, 1.85)	0.8		
Model 3: Continuous intended dose, effect modification by type of surgery (N=8,879)§									
	Effect modifier								
Trend per Gy	BCS		442/6,906	1.05	0.09	(0.88, 1.25)	0.6	-	-
	Mastectomy		136/1,973	1.09	0.11	(0.90, 1.32)	0.4	-	-

* Wald test of association with outcome, separately for each category of variable, on one degree of freedom.
† Joint likelihood ratio test of association with outcome, of variable including all *n* categories, on (*n* -1) degrees of freedom.
‡ Wald test for linear trend across variable.
§ Model adjusted for chemotherapy, surgery, grouped age, number of nodes involved, stage, morphology, HER 2 treatment, and continuous calendar period in years.
¦ Model adjusted for continous age in years, number of nodes involved, continuous calendar period in years, trend across social deprivation quintiles.

Abbreviations: BC=breast cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number. IMD=indices of multiple deprivation. BCS=breast conserving surgery. HER-2=human epidermal growth factor receptor 2.

For the purpose of comparing with other outcomes and for assessing any linear trend, Model 3 shows results for intended EQD2T in continuous rather than categorical form. Effect modification by type of surgery was also included. Though intended EQD2T as a categorical variable was associated with non-breast-cancer survival, in its continuous form there was no association, either among BCS patients (HR 1.05, 95% CI 0.88-1.25, p=0.6) or among mastectomy patients (HR 1.09, 95% CI 0.90-1.32, p=0.4).

3.3.2.d Analysis by treatment centre

In a separate analysis, differences were assessed in hazard of a breast cancer event by treatment centre, with Oxford as the baseline (Table 4.25, Model 1). Radiotherapy dose was not included in the model, but all other co-variates were the same as for analyses of intended EQD2T. While Reading and Leicester had very similar hazards of a breast cancer event compared to Oxford, patients in Northampton were more likely to develop a breast cancer event (HR 1.23, 95% CI 1.12-1.35, p<0.0001). Patients in Mount Vernon may have been somewhat more likely to develop a breast cancer event, but this was not statistically significant (HR 1.10, 95% CI 0.98-1.25, p=0.1). The strong association with a breast cancer event seen in Northampton was most likely due to the fact that in Northampton most patients received 45 Gy in 20 fractions (Figure 4.8). Patients who received this regimen did less well than most other treatment groups in models of categorical dose (Table 4.21). The effect of centre was therefore likely explained by the differences in fractionation between centres.

Adjusting for both centre and fractionation at once was considered to be over-adjustment, as the variation in fractionation was highly significantly correlated with treatment centre (Table 4.25, Model 2). Adjusting for both at once, there was a weak association of intended dose and hazard of a breast cancer event (p=0.02, p for trend=0.05), while the effect of centre disappeared (p=0.6).

Table 4.25: Hazard of breast cancer event by treatment centre (N=8,879)

	No. events/ patients	HR	SE	95% CI	p_{Wald}*	Joint p_{LR}†	p_{Wald}‡ trend
Model 1: Treatment centre without inclusion of EQD2T§							
Treatment Centre							
Oxford	938/3,125	1				0.0002	-
Reading	321/1,077	0.99	0.07	(0.87, 1.13)	0.9		
Northampton	888/2,658	1.23	0.06	(1.12, 1.35)	<0.0001		
Mount Vernon	361/1,224	1.10	0.07	(0.98, 1.25)	0.1		
Leicester	235/795	0.98	0.12	(0.78, 1.23)	0.8		
Model 2: Overadjustment: both treatment centre and EQD2T included¦							
Treatment Centre							
Oxford	938/3,125	1				0.6	-
Reading	321/1,077	1.00	0.09	(0.84, 1.18)	0.98		
Northampton	888/2,658	1.11	0.09	(0.95, 1.30)	0.2		
Mount Vernon	361/1,224	1.07	0.09	(0.90, 1.27)	0.5		
Leicester	235/795	0.94	0.25	(0.56, 1.59)	0.8		
EQD2T (Gy), Total dose (Gy) in no. fractions¶							
43.5, 45 in 20 (L)	95/177	1.39	0.37	(0.83, 2.34)	0.2	0.02	0.05
43.6, 50 in 25 (L)	122/533	0.86	0.22	(0.53, 1.42)	0.6		
44.2, 45 in 20 (N)	573/1,634	1.11	0.09	(0.95, 1.30)	0.2		
44.4, 40 in 15	839/3,026	1					
44.6, 50 in 25	471/1,326	1.00	0.07	(0.87, 1.15)	0.99		
45.4, 41.6 in 13 (O)	563/1,989	0.95	0.08	(0.80, 1.12)	0.5		
46.8, 40 in 12 (R)	80/194	0.85	0.12	(0.64, 1.11)	0.2		

* Wald test of association with outcome, separately for each category of variable, on one degree of freedom.

† Joint likelihood ratio test of association with outcome, of variable including all *n* categories, on (*n* -1) degrees of freedom.

‡ Wald test for linear trend across variable.

§ Model adjusted for chemotherapy, surgery, grouped age, number of nodes involved, stage, morphology, HER-2 treatment, and continuous calendar period in years

¦ Model also adjusted for chemotherapy, surgery, grouped age, number of nodes involved, stage, morphology, HER-2 treatment, and continuous calendar period in years.

¶ L=Leicester, N=Northampton, O=Oxford, R=Reading, MV=Mount Vernon

Abbreviations: BC=breast cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number. IMD=indices of multiple deprivation. BCS=breast conserving surgery. HER-2=human epidermal growth factor receptor 2.

3.4 Ductal Carcinoma in Situ

3.4.1 Descriptive analyses

There were 477 eligible DCIS patients[12], 185 (39%) of whom were treated in Northampton. Treatment patterns for DCIS and invasive patients were similar in Northampton and Mount Vernon, but differed in Oxford, Reading and Leicester (Figure 4.12 for DCIS patients, compare to Figure 4.8 for invasive patients). In Northampton, the commonest fractionation for DCIS patients was 45 Gy in 20 fractions (111/185 patients), while in Mount Vernon it was 40 Gy in 15 fractions (70/72 patients). Whereas most invasive patients in Oxford had been treated with 41.6 Gy in 13 fractions, most DCIS patients received 50 Gy in 25 fractions (56/105 patients). In Reading, most invasive patients received 40 Gy in 15 fractions, while most DCIS patients received 50 Gy in 25 fractions (44/76 patients). In Leicester, the commonest fractionation for both invasive and DCIS patients was 50 Gy in 25 fractions (34/39 DCIS patients), but invasive patients had also been treated with 45 Gy in 20 fractions while no DCIS patients were treated with this fractionation. Only 12% of DCIS patients received any radiotherapy boost, and most of these patients were in Mount Vernon and Northampton. Eleven patients had a record of a non-standard number of fractions (details not shown).

Between 2004 and 2007, the fractionations most commonly used were 50 Gy in 25 fractions and 45 Gy in 20 (Figure 4.13). By 2008-09, the convention became 40 Gy in 15, and this was the predominant fractionation in 2010-11. As was the case for invasive BC patients, there was a range of total number of treatment days over which DCIS patients received any given fractionation (Figure 4.14).

Only 35/477 patients (7%) developed an invasive BC, the outcome of interest for the DCIS analysis. With so few events, it is not surprising that there were no associations seen between

[12] Six of the 477 patients (1%) had a record of non-ductal carcinoma in situ. Considering the overwhelming proportion with ductal disease, it is referred to as ductal carcinoma in situ rather than carcinoma in situ of the breast.

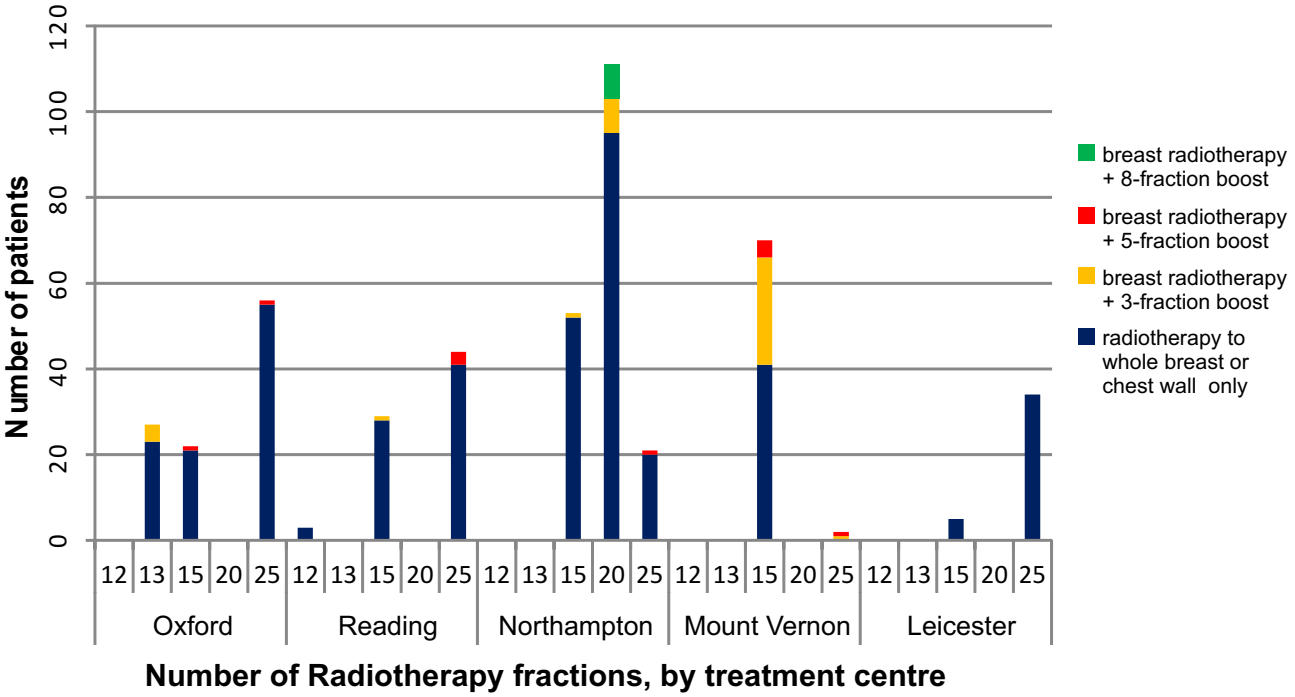


Figure 4.12: No. of DCIS patients by radiotherapy fractions delivered to the whole breast or chest wall, for each centre

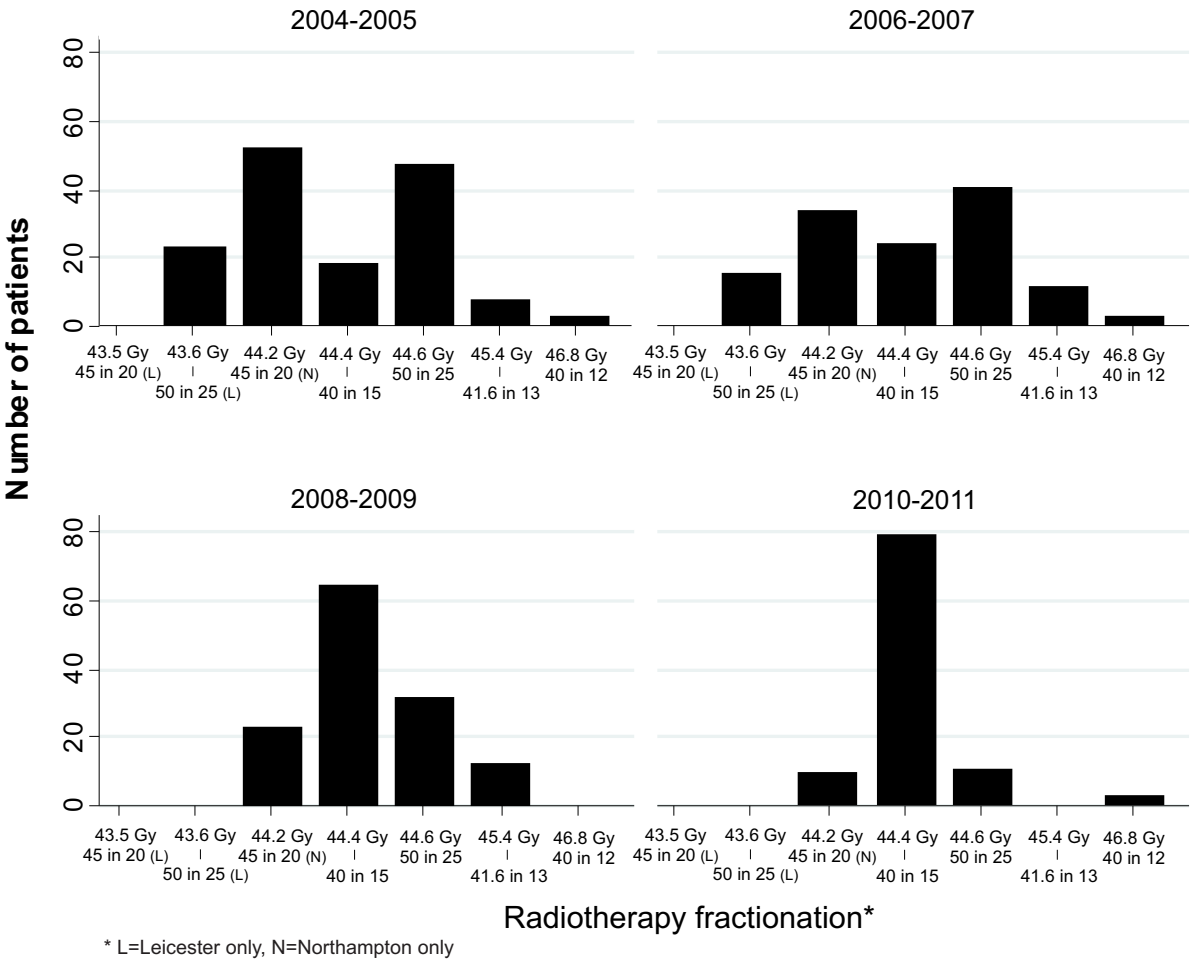


Figure 4.13: Number of DCIS patients treated by radiotherapy fractionation, over calendar period

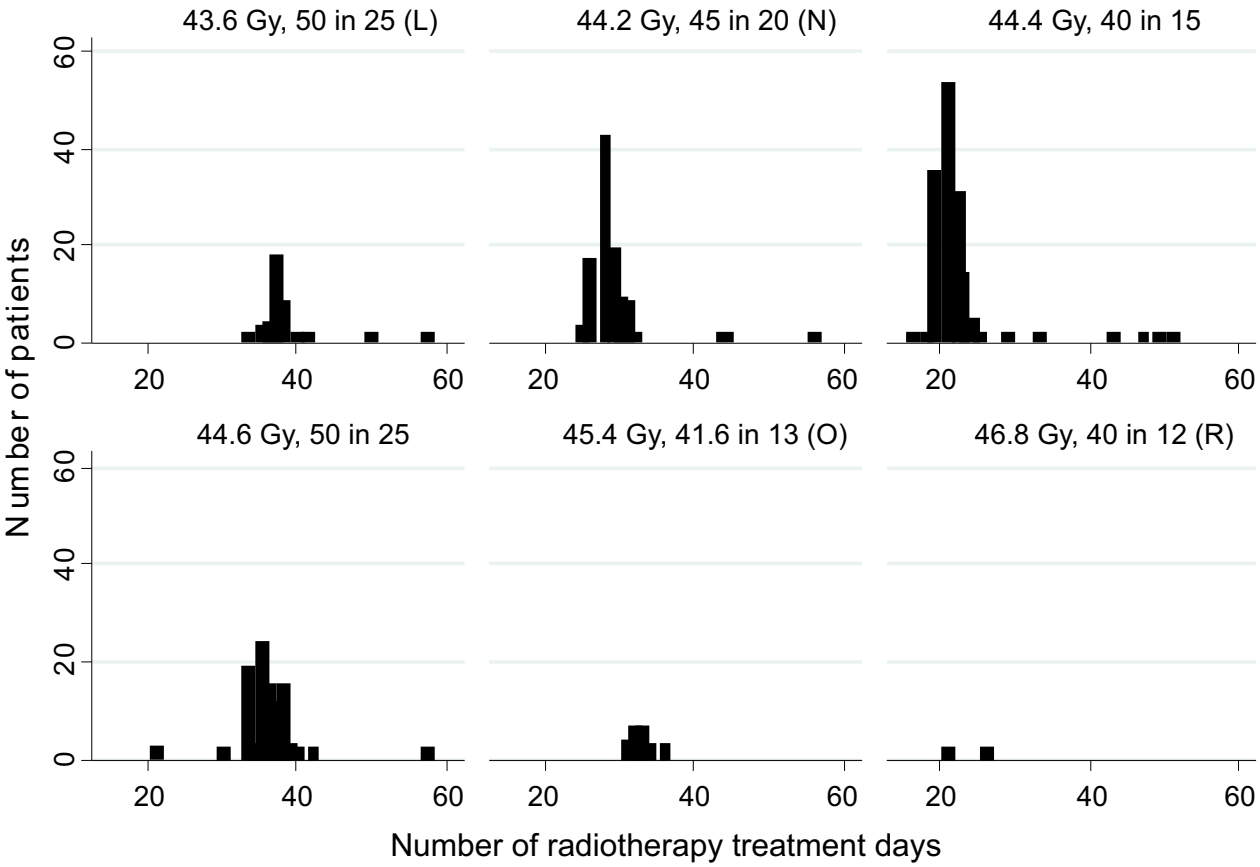


Figure 4.14: No. of DCIS patients treated by no. of treatment days for each radiotherapy fractionation. L=Leicester only, N=Northampton only, O=Oxford only, R=Reading only. Data for patients with more than 60 treatment days are not displayed.

developing an invasive BC and either intended EQD2T (p=0.9) or any other variable one might include as a potential confounder or effect modifier (Table 4.26). There were associations between intended EQD2T and receipt of any radiotherapy boost (p=0.007), treatment centre (p<0.001), age at diagnosis (p=0.02), calendar period (p<0.001), surgery type (p<0.001), and receipt of hormone therapy (p<0.001).

Despite a mean follow-up time of 8.6 years, it was not possible to conduct any multivariable analyses of an association between radiotherapy fractionation and hazard of invasive BC, due to the low number of events.

Table 4.26: Descriptive characteristics of DCIS patient population

	Total no. patients	Mean (SD)	Invasive breast cancer %	Invasive breast cancer p*	Intended EQD2T p*
All patients	477		7	-	-
Follow-up time (years)					
Invasive breast cancer		8.6 (2.8)			
Intended EQD2T dose to whole breast (Gy), Total dose (Gy) in no. fractions†					
43.5, 45 in 20 (L)	0	44.4 (0.4)	0	0.9	-
43.6, 50 in 25 (L)	34		3		
44.2, 45 in 20 (N)	111		8		
44.4, 40 in 15	179		8		
44.6, 50 in 25	123		7		
45.4, 41.6 in 13 (O)	27		7		
46.8, 40 in 12 (R)	3		0		
Radiotherapy boost					
None	418		7	0.2	0.007
Any	59		12		
Treatment Centre					
Oxford	105		9	0.9	<0.001
Reading	76		9		
Northampton	185		6		
Mount Vernon	72		7		
Leicester	39		5		
Age (years)					
20-49	50	58.7 (8.5)	12	0.5	0.02
50-59	201		7		
60-69	184		7		
70+	42		5		
Social deprivation (quintiles of IMD score)					
Least deprived	224		8	0.8	0.1
2nd	116		9		
3rd	72		7		
4th	48		6		
Most deprived	17		0		
Calendar period					
2004-2005	139		7	0.7	<0.001
2006-2007	117		7		
2008-2009	125		10		
2010-2011	96		5		
Cytotoxic Chemotherapy					
No	473		7	0.6	0.9
Yes	4		0		
Surgery type					
BCS	463		8	0.3	<0.001
Mastectomy	14		0		

Table continued on next page.

Table 4.26 continued.

	Total no. patients	Mean (SD)	Invasive breast cancer %	Invasive breast cancer p*	Intended EQD2T p*
Hormone therapy					
Unknown	432		8	0.4	<0.001
Yes	45		4		
HER-2 treatment					
Unknown	477		35	-	-
Yes	0		0		

* Chi squared test of overall association.
† L=Leicester, N=Northampton, O=Oxford, R=Reading, MV=Mount Vernon

Abbreviations: SD=standard deviation. EQD2T=time-corrected equivalent dose in 2 Gy fractions. IMD=Indices of Multiple Deprivation.BCS=breast conserving surgery.

4 Discussion & Conclusions

It is known that higher radiotherapy dose results in increased tumour cell kill (39). However, it is not known whether fractionations resulting in a higher EQD2T are associated in improved outcomes, as the benefits of radiotherapy may be outweighed by the risks at higher doses. There may be thresholds of dose above which radiotherapy becomes too toxic to normal surrounding tissues. The meta-analysis of randomised trials in NSCLC (Chapter 2) showed that in patients who did not receive chemotherapy, such a threshold does not appear yet to have been reached in NSCLC. However, when combined with concurrent chemotherapy, the toxicity of both treatments may result in poorer survival at higher radiotherapy doses. Perhaps, in the studies included in this meta-analysis, a dose threshold in combined radiotherapy and chemotherapy dose may have been reached. Advances in radiotherapy and chemotherapy resulting in a reduction in toxicity could, in the future, raise the dose threshold that may be tolerated by patients.

There are two epidemiological approaches to studying the question of whether two or more radiotherapy fractionations of different biologically effective dose differ in terms of patient outcomes. One is the randomised controlled trial, which has the advantage of eliminating confounding in the groups being compared. The disadvantages of randomised controlled trials are that they are expensive, take a long time, and patients included are highly selected and do not represent the whole population of patients treated with radiotherapy for the same cancer.

The other epidemiological approach is the observational study. There are different types of observational study, but in this thesis a cohort study was conducted using population-based cancer registration data collected in the past. Many years of follow-up time had already been accrued for these patients. The advantage of this study type was that it was likely to be representative of the cancer population receiving radiotherapy of curative intent in England and that enough follow-up time had been accrued by the time of analysis. The potential disadvantage of an observational study could be confounding between the groups being compared, if

insufficient information on confounders had been obtained. The effect on survival of different radiotherapy dose-fractionations was likely to be small, and confounding could mask a small effect. In this study, the aim was to ask whether radiotherapy dose-fractionation results in different patient outcomes. But an additional aim was to determine whether it is possible to examine such a question in an observational study, given the potential for confounding.

This is the first study to use English cancer registration data to analyse effects of radiotherapy dose-fractionation. Despite logistical challenges, multiple data sources were brought together to produce a good quality dataset for analysis. There was great potential in using English cancer registration data between 2004 and 2011 to study different dose-fractionations due to the variability in radiotherapy practices in the same clinical situation between and within treatment centres during this period.

However, it was found that unaccounted patient selection factors were present both in NSCLC and invasive BC analyses, and that these probably differed by treatment centre. The main conclusion of this study was that it is not possible to use these observational data to answer questions about different radiotherapy dose-fractionations.

4.1 Non-small cell lung cancer

4.1.1 Association of intended EQD2T and lung-specific survival, overall survival, and hazard of second cancers

The main outcome examined for NSCLC was lung-specific survival. Overall, there was no trend in lung-specific survival with increasing radiotherapy dose (HR 0.99, 95% CI 0.93-1.05, p=0.8, Table 4.10). However, there were important effect modifications by treatment centre (p=0.0007) and by receipt of chemotherapy (p=0.02). Among patients who received no chemotherapy, there was an *increase* in survival the higher the intended EQD2T (HR 0.91, 95% CI 0.83-1.00, p=0.05). Among patients who did receive chemotherapy, there was a possible *decrease* in survival with higher

intended EQD2T (HR 1.05, 95% CI 0.97-1.15, p=0.2). This result is consistent with the result obtained in the meta-analysis (Chapter 2).

However, the more important effect modification was by treatment centre. A final model included effect modification by both chemotherapy and treatment centre. Had there been any causal association between radiotherapy dose fractionation and lung cancer survival, there should have been similar trends across increasing dose within chemotherapy treatment groups, regardless of treatment centre. However, this was not so. In Oxford and Leicester, trends were not statistically significant, though there may have been a small benefit in increasing dose among patients who did not receive chemotherapy (Table 4.10, Model 4). In Reading, there may also have been a benefit of higher dose, and this was statistically significant among patients who did not receive chemotherapy (No chemotherapy: HR 0.81, 95% CI 0.66-0.99, p=0.04 versus Chemotherapy: HR 0.88, 95% CI 0.74-1.04, p=0.1). However, in Northampton, the opposite was true. There was an *increase* in hazard of NSCLC with increasing intended EQD2T, and this was statistically significant among patients who received chemotherapy (No chemotherapy: HR 1.05, 95% CI 0.82-1.36 versus Chemotherapy: HR 1.21, 95% CI 1.04-1.41, p=0.01).

The fact that these results were not consistent with one another make it unlikely that the estimates obtained were due to the effect of dose. A more likely explanation for the trends seen is patient selection. At some centres it appears that patients with a poorer prognosis may have received a lower dose, for example in Reading. In Northampton, patients with a poorer prognosis appear to have been selected to receive a higher dose. This could mean that were one to add data such as these from other centres in the UK, there may be other, unpredictable trends in increasing dose, dependent on the protocols at a given centre.

Nonetheless, it may be possible that in this final model a detrimental effect could still be seen of increasing radiotherapy dose in patients who received chemotherapy compared to patients who did not receive chemotherapy. The trends with increasing dose among patients who received

chemotherapy were different between centres. However, *within centre*, when comparing the trends among patients who did not receive chemotherapy to those who did receive chemotherapy, in each case, patients who did receive chemotherapy did worse at higher radiotherapy doses than patients who did not receive chemotherapy (Table 4.10, Model 4).

Examining intended EQD2T as a categorical variable was underpowered, but it appeared that patients who received the CHART regimen may have had poorer lung cancer survival than patients who received 55 Gy in 20 fractions (p=0.09, Table 4.10, Model 5). The CHART trial had as a comparison arm 60 Gy in 30 fractions, which is a lower EQD2T than CHART, while 55 Gy in 20 fractions is a higher EQD2T. It is probable that patient selection may have accounted for the worse survival of CHART patients. In Oxford, patients who were less fit generally were selected to receive CHART rather than 55 Gy in 20 (Geoff Higgins, personal communication).

Sensitivity analyses showed that trends across increasing dose were similar, using actual EQD2T compared to intended EQD2T (Table 4.13, Model 1act versus Model 1int). It therefore appears that the assumptions made about number of intended fractions and average number of treatment days were acceptable.

Lung-specific and overall survival results were consistent (Tables 4.10 and 4.14). In a model including effect modification by chemotherapy and treatment centre, higher dose appeared to be protective among patients who did not receive chemotherapy in Reading, both in terms of lung-cancer survival and overall survival. And higher dose appeared to be harmful among patients who received chemotherapy in Northampton, both in terms of lung cancer survival and overall survival. This consistency in results in lung cancer survival and overall survival is no surprise as 86% of all deaths were lung cancer deaths. This is useful information for the meta-analysis: in that study it was assumed that all patients had died of lung cancer. It appears that making such an assumption was acceptable, in the absence of cause of death information.

There was not enough information on second cancers (22 events) to draw any conclusions about hazard of second cancers and radiotherapy fractionation.

4.1.2 Association of other variables with lung-specific and overall survival

4.1.2.a Variables available for all NSCLC patients

Two co-variates were clearly associated with lung-specific and overall survival: sex and calendar period. Females survived better than males, and survival outcomes worsened over calendar period. Perhaps there were other factors not accounted for that confounded the association between female sex and survival; however, in the Oxford-only models that included current smoking status and comorbidity, while sex was no longer as strongly associated with survival, women still did better than men. This finding is supported by other studies on differential survival in NSCLC patients by sex (41, 42).

In this study, lung-specific and overall survival worsened over the calendar periods 2007-2009 and 2010-2011 as compared to 2004-2006. This is a surprising result, because in national statistics that include all lung cancer patients, lung cancer survival has seen modest improvement over the past few decades (43). NSCLC staging changed over this period, as more patients were categorised as later-stage with improved detection of cancer spread. But this should mean that over time more patients received palliative care who were previously incorrectly categorised as earlier-stage, and therefore patients receiving curative care should have survived better, simply due to stage migration. It is possible, however, that with increasing use of modern (conformal) radiation techniques, patients with more comorbidities may increasingly have been given curative-intent treatment, in the hope that their outcomes could be better than with palliative treatment. It is also possible that surgical practice has changed to include more patients in curative-intent surgery who would previously have received radiotherapy as their primary treatment. Those receiving curative-intent surgery would be the fittest patients who survive better, and their increasing exclusion from this study population would help to explain a reduction in survival over time.

4.1.2.b Other variables gained through perusal of patient notes

Though added variables from examining patient notes did appear to be confounders in a categorical model of intended EQD2T, they did not affect results of models with continuous EQD2T. In the categorical fully adjusted model including the 108 patients whose patient notes were reviewed, the four new variables smoking status, cancer stage, history of serious comorbidity and chemotherapy timing were confounders of the association between intended EQD2T and lung cancer survival (Table 4.11). However, in the final continuous model, the trend with increasing dose was not much different including or excluding these variables (Table 4.12, Model 1 versus Model 2). While smoking status did show an important independent association with lung cancer survival, it is not clear that excluding these variables from the main analyses had much impact on final results. It may be possible that these factors would have had more of a confounding effect in centres where trends in dose appeared to be steepest (Reading and Northampton).

4.1.3 Impact of errors discovered in CIA or CAS data

While there were some errors discovered either in treatment dates (CIA) or in whether patients had received curative surgery or chemotherapy (CAS treatment data), the overall impact of correcting these errors was negligible for results including all centres, and minor in results for Oxford-only data. Bigger changes to analyses were seen in the correction of assumptions made on non-standard numbers of fractions. The assumption had been that two patients were intended to receive lower doses than was indeed the case, and as these patients stopped their treatment early (poorer outcomes), the estimated trend in radiotherapy dose was originally steeper than it should have been (Table 4.10, Model 4a versus Model 4). Even so, the interpretation of results was unchanged. Overall, such assumptions on intended number of fractions were made for 4% of NSCLC patients (only 2% of breast cancer patients), so it is probable that results of this study are acceptable despite any incorrect assumptions.

Data on the number of fractions and on treatment dates came from the CIA project, which is now closed and unlikely to be used for much further analysis. The impact of errors found in CAS data is thus more important, as CAS data are being used increasingly. It is encouraging that for NSCLC patients in Oxford, if data were present, they tended to be correct. As the same data teams work on all cancer sites, it is plausible that CAS treatment data were of equally good quality for other cancer sites in Oxford. Data missingness did vary substantially between centres, but perhaps it is possible to surmise that if CAS treatment data are recorded, they can be trusted. It would be useful to conduct spot checks at other centres to corroborate this conclusion.

4.1.4 Results of this study compared to randomised trials

The results of this study were compared to results obtained from the meta-analysis of randomised trials. This cohort study does show that higher radiotherapy dose appears to be harmful for patients who also receive chemotherapy (see above). However, patient selection makes it impossible to draw any conclusions about the effect of radiotherapy dose in this study population.

It should be noted that in the meta-analysis of randomised trials, the range of EQD2T was from 36.4 Gy to 80.8 Gy with dose differences between trial arms of up to 27.2 Gy. EQD2Ts used at the centres in this study ranged from 48.8 Gy to 55.1 Gy, so perhaps with a wider range of doses, any true underlying effect of increasing dose might have been more easily detected in observational data, despite patient selection.

4.2 Invasive Breast Cancer

4.2.1 Association of intended EQD2T and hazard of breast cancer events, breast-specific survival, overall survival, and non-breast-cancer survival

The main aim was to assess whether there may be differences in the hazard of developing a breast cancer event by radiotherapy dose-fractionation. Simpler models with intended EQD2T as

continuous were tested against more complex models with EQD2T as categorical, and the categorical models were found to be a better fit to the data. More complex models including effect modifications were also tested against simpler models without effect modification. The model that best fit the data was one in which each type of fractionation was presented categorically including information on boost, and with effect modification by type of surgery and treatment centre (Appendix 3, Table 2). This model contains 42 categories of EQD2T within effect modification groups. Such a model is exceedingly difficult to interpret, but it does show that there was a great degree of heterogeneity between all of these groups.

If there were a plausible causal association between radiotherapy dose-fractionation and hazard of a breast cancer event, one might expect there to be a trend across increasing dose. Indeed, this appears in the first instance to be so, with an overall hazard ratio of 0.88 per Gray increase in dose (95% CI 0.83-0.94, Table 4.20). However, including effect modification by type of surgery and treatment centre resulted in a similar scenario to NSCLC analyses: there were different trends dependent on treatment centre (Model 4, Table 4.20). Among mastectomy patients in Oxford there appeared to be a benefit in increasing dose, but this was not the case for BCS patients. Conversely, BCS patients in Reading appeared to suffer an increase in hazard of a breast cancer event with increasing dose, while there was no detectable effect among mastectomy patients. In Northampton, there appeared to be huge benefit in increasing dose, while again there was no effect among mastectomy patients. In Leicester, no effects could be detected, and in Mount Vernon the range of radiotherapy dose was so narrow, no reliable effect estimates could be obtained.

This lack of consistency between the centres and surgery types shows that there was unlikely to be an overall effect of intended EQD2T and hazard of any breast cancer event. Such a degree of heterogeneity between the categories of patient suggests patient selection.

Protocols in Oxford and Reading reveal some of the patient factors likely to be present in this patient population (Oxford University Hospitals Breast radiotherapy protocols 2002-2010; and Dr Ruth Davies, Consultant Oncologist, Royal Berkshire Hospital, personal communication). For most of the study period, in Oxford, 50 Gy in 25 daily fractions or 40 Gy in 15 daily fractions were only to be used for DCIS patients, patients with very large breasts, patients with severe underlying lung disease, patients with severe underlying cardiac disease with left-sided tumours, and patients with any presence of reconstruction with implant or considered for any other reconstruction. Meanwhile, in Reading, the 50 Gy in 25 fraction regimen was only given to women after breast reconstruction if they had large breasts (not patients with severe lung or heart disease). It is difficult to access old protocols and even more difficult to contact radiation oncologists who were working at these centres at the time of this study, so it is not possible to know the full heterogeneity of patient selection.

There is, however, further evidence of patient selection within the data. Firstly, the fact that different centres offered such different radiotherapy dose fractionations and that the proportion of patients receiving a given dose-fractionation varied so greatly, indicates underlying differences in how patients with different profiles must have been treated. The best evidence, however, is the strength of association between intended EQD2T and *non-breast-cancer* survival. Any possible deaths due to late effects of radiotherapy were categorised as breast cancer deaths, so none of these non-breast-cancer deaths should be due to the radiotherapy they received. It is likely that patients who died of other causes already presented at cancer diagnosis with illnesses that later caused their death. However, their reduced fitness likely caused their radiation oncologist to select a certain radiotherapy dose-fractionation deemed more suitable for frail patients. There was no linear trend in the association of non-breast-cancer survival with radiotherapy dose, but a very strong association when intended EQD2T was analysed *categorically*. This is further evidence of patient selection rather than any underlying causal relationship.

There does not appear to be any linear association between breast-cancer survival and intended EQD2T (BCS: HR 1.07, 95% CI 0.91-1.24; mastectomy: HR 0.93, 95% CI 0.82-1.06). This suggests that results seen for breast cancer events were driven primarily by recurrences, metastases, and contralateral breast cancers. Results for overall survival were very similar to breast cancer survival.

4.2.2 Sensitivity analyses

Including information on breast boost dose, excluding patients for whom assumptions on intended number of factions had been made and whose number of treatment days were outside a standard range did not change results materially (Table 4.22). Using "actual" radiotherapy dose information also did not greatly affect breast cancer event analyses (Table 4.22). Therefore assumptions on intended dose and average number of treatment days were probably acceptable. Encouragingly, censoring events at age 75 resulted in very little impact, suggesting that over-diagnosis of breast cancer as underlying cause of death did not greatly impact results (Table 4.22). There was no interaction by presence of positive lymph nodes, and results obtained by type of surgery were not materially different by whether disease had spread to the lymph nodes (Table 4.22).

4.2.3 Factors associated with breast cancer events, breast cancer survival and non-breast-cancer survival

As expected, patients in the middle age range of 50-70 suffered the least hazard of any breast cancer event or of breast cancer death, compared to younger and older patients (Table 4.19). The greater the number of nodes involved and the more advanced the stage, the more likely patients were to experience a breast cancer event (trend also present just for breast cancer death, though slightly less significant). Compared to patients with ductal carcinomas, patients with tubular breast cancer had half the hazard of developing a breast cancer event, and only a quarter the hazard of a breast cancer death. Patients with mucinous breast cancer also had about half the

hazard of experiencing either any breast cancer event or breast cancer death. These findings on histological subtype have been confirmed in other studies (44). While there was an increase in the hazard of a breast cancer event over calendar period (HR 1.03, 95% CI 1.01-1.06, p for trend=0.01), the opposite was true for breast cancer death (HR 0.91, 95% CI 0.87-0.95, p for trend<0.0001). This is because recording of breast recurrences has been steadily improving over time, and therefore it appears that there are more recurrences when in fact this is unlikely to be the case.

Patients receiving chemotherapy had a higher hazard both of any breast cancer event and of breast cancer death. This was probably not caused by the chemotherapy; rather, patients who receive chemotherapy are at higher risk of such outcomes and are in need of systemic therapy (described in the Background to this chapter). Mastectomy patients also had worse breast cancer outcomes, in particular breast cancer death (HR 1.72, 95% CI 1.49-1.99), which is not surprising given patient selection for type of surgery (15, 16). Results for hormone therapy and HER-2 treatment should be interpreted with caution, because there was likely an underestimation of patients who had either therapy, and again, patient selection may affect interpretation of the results. It is curious, however, that patients who received HER-2 treatment seemed possibly to be at a lower risk of breast cancer death while they had a much higher hazard of any breast event (HR breast cancer death 0.82, 95% CI 0.52-1.31 versus HR any breast event 3.40, 95% CI 2.82-4.11).

Associations between these co-variates and non-breast-cancer death were very different, as is no surprise. Older patients were much more likely to die, with 80+ year olds 16 times as likely to die as their 50-60-year old counterparts, and 20-40-year olds a quarter as likely to die. Breast cancer tumour or treatment-related factors (with the exception of radiotherapy dose) were not associated with non-breast-cancer death (radiotherapy boost, number of nodes involved, stage, morphology, chemotherapy, surgery type, hormone therapy, and HER-2 treatment). In contrast, level of social deprivation was strongly associated with non-breast-cancer death, with an 18%

increase in hazard per quintile of greater deprivation. Hazard of non-breast-cancer death decreased, with 8% less hazard per year between 2004 and 2011. This is likely to be due to advances in medicine that are prolonging life across the developed world (45).

4.2.4 Results of this study compared to randomised trials

Comparing the results of this study with those of randomised trials is difficult for a number of reasons. As patients entered into trials are highly selected and differ greatly to patients in the general cancer patient population, comparing results for overall survival would be biased, as patients in the general population are less fit than patients in randomised trials and more likely to die of causes other than breast cancer. It may be better to compare a breast-cancer specific result such as recurrence, though even this may be biased as patients entered into trials may also have a better breast cancer prognosis and therefore be less likely to develop recurrences. However, the principal challenge in comparing the results of this study with clinical trials of breast cancer is that recent big trials are specifically intended to have equivalent dose, rather than higher or lower dose. Trying to fit a trend in dose in a meta-analysis of breast cancer radiotherapy trials is thus not feasible.

The only comparisons one might consider are with the START A trial, which randomised patients to 50 Gy in 25 or 41.6 Gy in 13 (or 39 Gy in 13, not available in this study), and with the START B trial, which randomised patients to 50 Gy in 25 or 40 Gy in 15 (18). Both trials randomised only women who had had BCS. Ten-year results for these trials show that compared to 50 Gy in 25, the 41.6 Gy in 13 fractionation was equivalent, with a hazard ratio for any breast-cancer related event of 0.94 (95% CI 0.75-.17, p=0.6). Also compared to 50 Gy in 25, the 40 Gy in 15 fractionation did better, with a hazard ratio for any breast-cancer related event of 0.80 (95% CI 0.65-0.99, p=0.04). The difference in EQD2T between 40 Gy in 15 (44.4 Gy EQD2T) and 50 Gy in 25 (44.6 Gy EQD2T) is almost none, however, so any true benefit patients might have experienced is unlikely to be due to the radiotherapy dose.

To compare these results with this study, these same comparisons for breast-cancer events must be examined among women who have received BCS only. They can have received a boost, as patients in the START trials could also receive boosts. There was only one centre which gave 41.6 Gy in 13 fractions, which was Oxford. In an analysis with 50 Gy in 25 as the baseline (combining the Leicester group with the remaining centres despite a different EQD2T), the hazard ratio of 41.6 Gy in 13 versus 50 Gy in 25 was 0.95 (95% CI 0.83-1.07, p=0.4). Comparing results for 50 Gy in 25 fractions at each centre separately with the 41.6 Gy in 13 fractionation in Oxford, none of these comparisons was statistically significant, and the hazard ratios ranged from 0.63 (95% CI 0.37-1.09) in Mount Vernon to 1.21 (95% CI 0.93-1.58) in Leicester.

Every centre gave 40 Gy in 15 and 50 Gy in 25. Pooling results across centres, the overall hazard ratio for the 40 Gy in 15 versus 50 Gy in 25 fractionations was 1.06 (95% CI 0.93-1.19, p=0.4). Within each centre, none of the hazard ratios comparing 40 Gy in 15 to 50 Gy in 25 was statistically significant. Hazard ratios ranged from 0.67 (95% CI 0.39-1.16) in Mount Vernon to 1.17 (0.88-1.54) in Reading.

It is not possible to make any definitive conclusions about results from this cohort study compared to the START trial results. Drawing such comparisons is not appropriate given that results obtained in this study were driven by patient selection.

4.2.5 Analysis by treatment centre

An analysis by treatment centre, excluding radiotherapy dose from the model, showed a strong association between centre and hazard of a breast cancer event, with patients in Northampton having a worse outcome than patients at other centres. It is not surprising that such an association would be present given the association of intended EQD2T and hazard of a breast cancer event and the degree of heterogeneity between radiotherapy fractionations at the different centres. In addition, patient population characteristics are likely to differ at the different treatment centres, and patients in some areas may have worse outcomes than in other areas due

to non-treatment-related factors. It is not possible to conclude, therefore, that being treated in Northampton caused poorer outcomes.

4.3 Ductal Carcinoma in Situ

While there was also variability in radiotherapy fractionation evident in the treatment of DCIS patients, there were two few invasive BCs over this time period to conduct any analyses by radiotherapy fractionation.

4.4 NSCLC and invasive BC Analyses: points in common

Radiotherapy fractionation in the centres studied became less variable between centres over 2004-2011 for NSCLC and invasive BCs and also for DCIS. While initially 54 Gy in 36 (CHART) was given in Oxford and Leicester, by the end of the study period the most common regimen at all centres was 55 Gy in 20. Among breast and DCIS patients, the convergence to 40 Gy in 15 by 2010-11 was even clearer, after tremendous variability in fractionations between centres 2004 to 2007. This trend toward greater uniformity of practice in the UK is also supported by the 2016 RCR Dose Fractionation report, in which only 40 Gy in 15 is recommended for breast cancer (10). For NSCLC, 55 Gy in 20 is the main recommended regimen, though curiously CHART still remains a recommended regimen. The use of CHART, however, is debated and generally in less use.

The greatest point in common between the analyses conducted is that patient selection and differences in patient selection between centres appear to be a strong driving force in the results obtained. Were there a true underlying effect of radiotherapy dose, there would be a consistent trend in each of the outcomes studied. However, even if overall there appeared to be a trend for invasive BC patients in the hazard of a breast cancer event, there was a big interaction effect by centre. For both NSCLC and invasive BC, there were either flat or contradictory trends in hazard with increasing dose at the various centres.

4.5 Strengths and limitations

4.5.1 Strengths

The primary strength of this study is the length of follow-up. Few studies of invasive BC patients have as many events. Another strength is that most patients treated with radiotherapy of curative intent in the OCIU catchment area were likely to be included in this analysis. This area is on average less socially deprived than many other areas of England, but on the whole results could be seen as roughly representative of the UK. For both NSCLC and invasive BC, it is encouraging that associations observed between survival and factors other than radiotherapy fractionation were similar to those obtained in studies elsewhere.

Another strength of this study is the high quality of information on deaths and underlying causes as reporting of these is highly prioritised in the UK. Cancer sites are also very likely to be correctly diagnosed, given how meticulously this information is checked for each patient. Data on breast cancer surgery are also good, as these were supplemented with data from HES.

A further strength of this study is the possibility to make use of the brand-new initiative to develop an algorithm for determining breast cancer recurrence. Recurrences are more common than breast cancer deaths and are an important medical outcome that heretofore has not been possible to examine in analyses using UK cancer registration data outside the West Midlands (the registry in the West Midlands had a focus on breast cancer prior to the convergence of the eight English cancer registries).

Finally, it was possible to conduct sensitivity analyses to check whether assumptions made about intended number of fractions and treatment time for patients with non-standard data might be biasing results. The Oxford NSCLC patient notes sub-study did show that errors were likely to have been made in assumptions on intended numbers of fractions. However, radiotherapy treatment dates were on the whole likely to be correct (at least for patients in Oxford). The number of

patients with non-standard numbers of fractions appeared to be few and the impact of such errors likely to be minimal.

4.5.2 Limitations

The biggest limitation of the study is lacking information on important patient characteristics and other factors that may still confound analyses. Such patient selection factors include comorbidities, body mass index, tumour size, precise tumour location, breast size, presence of breast implants, any breast reconstruction surgery, stage (NSCLC), oestrogen receptor status (breast cancer), information on type of chemotherapy, and possibly others such as smoking status during radiotherapy and alcohol intake. There may also be other factors related to patient selection for either of these cancers, and there may be treatment-related factors such as radiotherapy field size that could systematically differ by centre. Any such systematic differences in treatment delivery may also help to explain some of the differences in dose seen between treatment centres.

In addition, some variables that are available were missing for many patients. These include stage, chemotherapy yes/no, and surgery status for both NSCLC and invasive BC, and number of nodes involved, hormone therapy, and especially HER-2 treatment for breast cancer. Missing information on these factors may bias results obtained.

Date information on cancer diagnosis was not always accurate. Some dates of diagnosis came after the radiotherapy start date indicated in the CIA dataset. This variable seems to be of less-good quality in the cancer registration dataset than information on type of cancer.

Another limitation of this study is the number of assumptions made in calculating intended EQD2T. Not only did some patients receive non-standard numbers of fractions, but it is not possible to know for certain whether those who had a record of having a standard number of fractions were in fact intended to receive this number or a different one. It may also be possible that some centres reported boost fractions for invasive BC patients more systematically than

others (e.g. none reported for Leicester patients). In addition there is the inherent limitation of the EQD2T formula used. The alpha-beta ratio for NSCLC may not be 10, and the time delay factor of 21 or k-factor of 0.6 may not be correct.

While the recurrence algorithm is a huge improvement on not having any information on recurrence, the algorithm is sure to have missed some recurrences, especially in the earlier years of this study period. As fractionation was strongly related to calendar period, results obtained for fractionation and hazard of a breast cancer event were biased. This means that hazards of fractionations more commonly used in the earlier years (eg 41.6 Gy in 13) were more underestimated than hazards of fractionations more commonly used in later years (eg 40 Gy in 15). There was no information on recurrence in NSCLC patients.

While a high proportion of NSCLC patients experienced events, the overall sample size was small. The effect of higher versus lower dose detected in the meta-analysis was small, suggesting that a much larger sample size would have been needed for this observational study. This was even more the case in DCIS analyses, which were not possible to conduct with so few events. A huge study would be needed for such analyses for DCIS.

Finally, institutional memory at hospitals was difficult to obtain. Access to historical treatment protocols at these centres is limited. Some are available in Oxford, but these are not always detailed on the subject of patient selection (no detail for NSCLC, some detail for breast patients). Communication with consultants at centres is also challenging, due to a heavy workload and frequent rotation of staff. Most consultants who treated these sites during this study period no longer work at these centres.

4.6 Conclusions

It is not possible to draw any conclusions about the effect of radiotherapy dose fractionation on long-term outcomes among NSCLC, invasive BC, and DCIS patients treated with radiotherapy of

curative intent, by means of an observational cohort study. It appears that patient selection was driving any differences seen in long-term outcomes. It is evident that the selection of patients for a given radiotherapy fractionation differed by treatment centre.

The main conclusion of this cohort study is thus that it was not possible to use observational data to obtain a reasonable estimate of the effect of radiotherapy dose fractionation on long-term outcomes in the treatment of cancer patients. Perhaps an observational study could work if all factors related to patient selection at the various treatment centres could be obtained and all such factors were known. Given the scope of such an effort, such a study would probably only be possible for a small number of patients. However, as the effect of radiotherapy dose-fractionation on long-term outcomes is likely to be small, such an analysis would require a large number of patients.

Radiotherapy fractionation in the UK has become more uniform over the past decade. Such a reduction in the variability of radiotherapy fractionation also limits any future analyses that could be done using observational data, even if confounding could be eliminated.

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Chapter 5

Overview of the Thesis, Further Research, and Summary

1 The need to study radiotherapy dose-fractionation

Radiotherapy has been one of the most important forms of cancer treatment for over a century and remains so today. While radiotherapy benefits many patients, the optimal dose and fractionation are not known. As discussed in **Chapter 1**, practices in radiotherapy dose-fractionation in use today were developed over a long period, but only in the last four to five decades have randomised trials been conducted. An international standard of around 2 Gy per fraction has been established based mostly on tradition, and this is the norm in most countries. In the United Kingdom, however, there has been greater diversity of practice, providing an opportunity to compare different dose-fractionation regimens.

Two cancer sites in which radiotherapy plays an important curative role are breast and lung. These two sites account for a large proportion of the cancer burden globally, especially in developed countries. In the UK, around 15% of new cancer cases are invasive breast cancers and 13% are lung cancers; 7% of all cancer deaths are from invasive breast cancer and 22% from lung cancer (1).

The question studied in this DPhil was whether different radiotherapy dose-fractionations are associated with differences in long-term outcomes in the curative treatment of NSCLC and breast cancer. Determining whether some fractionations are better than others could inform which fractionations are recommended in treatment guidelines. A secondary aim was to assess whether data from an observational study could be used to answer this question. If so, further observational studies could be recommended. These could be carried out relatively cheaply on large numbers of patients across all types of cancer that are treated by radiotherapy. If good quality data from patients treated in the past are available, it may be possible to conduct such studies quickly without having to wait many years for enough follow-up time to accrue.

To this end, two studies were conducted: a meta-analysis of randomised trials of radiotherapy dose-fractionation in NSCLC (**Chapter 2**), and a cohort study of NSCLC and breast cancer patients in the Thames Valley, using Public Health England cancer registration data (**Chapter 4**).

2 Studies of dose-fractionation in non-small cell lung and breast cancer

2.1 Meta-analysis of randomised trials in non-small cell lung cancer: Chapter 2

No randomised trials of radiotherapy dose and fractionation in NSCLC have included more than 600 patients, and many have fewer than 200. Consequently, most have not, individually, had sufficient power to detect modest effects on survival which would be important clinically. Combining results in a meta-analysis thus enables smaller differences to be detected reliably. The meta-analysis performed in this DPhil has, for the first time, included information from all relevant trials since 1980 and has compared trials by converting total doses to time-corrected equivalent doses in 2 Gy fractions.

Pooling data from trials that randomised patients to different radiotherapy dose-fractionations showed that when radiotherapy was given without chemotherapy, escalating radiotherapy dose led to improved survival in NSCLC patients treated with curative intent. In 18 trials in which no protocol chemotherapy was administered, radiotherapy dose escalation improved overall survival (median survival ratio: 1.13, 95% CI 1.04-1.22), corresponding to a survival gain of approximately two months for patients in these trials. The survival improvement increased progressively as the difference between EQD2T in the two trial arms increased and, in trials in which the difference was >10 Gy EQD2T, the median survival ratio was 1.47 (95% CI 1.23-1.75). This suggests that an upper radiotherapy dose threshold in patients treated with radiotherapy only has not been reached.

In five trials in which patients were treated with radiotherapy and concurrent chemotherapy, increasing radiotherapy dose led to a decrease in survival (median survival ratio 0.83, 95% CI 0.71-0.97, p=0.02). This suggests that risks of increasing radiotherapy dose outweigh benefits when concurrent chemotherapy is given. This decrease in survival was probably due to the combined

toxicity of radiotherapy and chemotherapy. However, modern radiation techniques are being developed to reduce doses to the normal lung tissue and heart, including intensity-modulated radiotherapy, proton beam therapy, and personalised isotoxic radiotherapy. In future, these efforts to reduce the toxicity of radiotherapy, together with an ongoing search for the optimal concurrent chemotherapy regimen, may enable radiotherapy dose to be escalated safely, even when concurrent chemotherapy is also given (2-4).

The principal aim of this meta-analysis was to determine whether different dose-fractionated regimens led to differences in survival. However, these data were also used to explore whether it matters how different radiotherapy doses are converted to equivalent doses in 2 Gy fractions, so that they can be compared.

Equivalent dose in 2 Gy factions can be calculated with or without incorporating information about overall treatment time. Both of these methods of calculation are accepted, though it is common to leave out the time factor. For the meta-analysis, the time factor was incorporated into calculations of EQD2T. To investigate whether the time factor was important, the main analyses were repeated using EQD2 omitting the time factor. This revealed that the conclusions of the meta-analysis would have been substantially different had a calculation without a time factor been used.

This leads to the question: is it better to include a time factor? Trial arm comparisons that were particularly affected by the new calculation without the time factor were comparisons in which one arm was hyperfractionated and accelerated and the other arm was not. In hyperfractionated-accelerated radiotherapy regimens, the overall treatment time is often less than in conventional regimens. However, toxicity was often higher in hyperfractionated-accelerated arms of trials in this meta-analysis in which one arm was hyperfractionated-accelerated and the other arm was not (5-9). This suggests that the biologically effective dose was probably higher in the hyperfractionated-accelerated regimens. However, when equivalent dose was recalculated without taking into account the total treatment time, hyperfractionated-accelerated regimens

were lower-dose than conventional ones. This comparison of results between the two types of calculation therefore provides support for use of a time factor in calculating equivalent dose in 2 Gy fractions in the design of new clinical trials.

2.2 Cohort study of patients in the Thames Valley

The meta-analysis described above showed that differences in dose led to differences in outcomes in randomised trials. In the second study in this DPhil, it was explored whether similar results could be obtained using observational data.

2.2.1 Chapter 3: developing the study

In this DPhil, data for a cohort study were brought together from multiple sources, including information on radiotherapy, patient outcomes, and potential confounders, to study the association between different radiotherapy dose-fractionations and patient outcomes. Chapter 3 explained how this was done and the hurdles which had to be overcome. This project started at a time when the new Public Health England was coming into being and eight separate English cancer registries were brought together as one. Despite the challenges, in part caused by this re-organisation, it was possible to produce a dataset with a wide range of important variables. It was not possible to obtain large-scale additional information directly from hospitals for all patients in this study. The main barrier to obtaining such information was the lack of NHS number identifiers attached to patients' hospital records. However, despite challenges in locating hospital data, it was possible to use information from the hospital records of 108/148 NSCLC patients treated in Oxford.

Chapter 3 highlighted the challenges that had to be overcome to conduct this cohort study. Based on the achievements of this DPhil, researchers should feel encouraged in future to use Public Health England data, despite the effort required to bring data together and time spent on data management. Use of data on a large scale obtained directly from hospitals, however, may not be

possible unless new mechanisms are developed to match patients to their records, or new ways are found to trace NHS numbers.

2.2.2 Chapter 4: using observational data to study radiotherapy dose-fractionation in non-small-cell lung cancer, invasive breast cancer, and ductal carcinoma in situ

After data for the cohort study had been collated and prepared for analyses, survival analyses were conducted to determine associations between radiotherapy dose-fractionations and the following outcomes:

(1) NSCLC: lung-cancer-specific survival and the development of new non-lung second primary cancers
(2) Invasive breast cancer: development of any breast-cancer-related event, breast-cancer-specific survival, and overall survival
(3) DCIS: development of invasive breast cancer

In NSCLC, there was no detectable difference in lung cancer survival between fractionations, regardless of whether EQD2T was analysed in continuous or categorical form. There was, however, a substantial difference of effect by treatment centre. Results for EQD2T in continuous form showed that in some centres increasing radiotherapy dose was associated with better survival. In other centres, it was associated with poorer survival, and these differences between centres were unlikely to be due to chance. Such opposite trends in effect are medically implausible, because if higher dose is beneficial, this should be so regardless of treatment centre. These opposite trends suggest that differences in patient selection between the centres were driving these results.

An additional question explored in the NSCLC analyses was whether there was a differential effect of radiotherapy dose, depending on whether chemotherapy was also given. This question was explored, because of the striking differences in effects observed in the meta-analysis in Chapter 2.

Indeed, there was a difference also for NSCLC patients in the cohort study, by whether or not chemotherapy was given. In each comparison within centre, patients who did not receive chemotherapy had better survival outcomes at higher radiotherapy doses compared to lower radiotherapy doses, than patients who did receive chemotherapy. This finding is consistent with the results of the meta-analysis, in which higher radiotherapy dose was beneficial only among patients who did not also receive chemotherapy.

In invasive breast cancer, analysing EQD2T in 42 separate categories showed significant heterogeneity between them. Analysing EQD2T in continuous form did show an apparent benefit of increasing dose, but there was a large difference in effect by treatment centre, and this difference was unlikely to be due to chance. As was the case for NSCLC, in some centres increasing radiotherapy dose was associated with better survival but in others it was associated with poorer survival. Patient selection therefore appears to explain differences in outcomes both for NSCLC and for invasive breast cancer. Comparing results with trials in invasive breast cancer was not possible, as recent trials have compared fractionations with very similar EQD2Ts. It was not possible to conduct survival analyses for DCIS, given the small number of primary invasive breast cancers subsequently developed by these patients.

Over the period of this study (2004-2011), the variability in fractionations given to NSCLC, invasive breast cancer, and DCIS patients reduced substantially. The NSCLC fractionation most commonly given at the end of the study period was 55 Gy in 20 fractions, while most invasive breast cancer and DCIS patients received 40 Gy in 15 fractions. This reduction in variability in UK practice is reflected in the reduction in the number of regimens in UK radiotherapy treatment guidelines published in 2016 compared to those published in 2006 (2, 10).

The main conclusion of this cohort study was therefore that it was not possible to use observational data to estimate the effects of radiotherapy dose fractionation on long-term outcomes. Factors affecting patient selection that were not available in this study probably

explain differences seen in outcomes from different radiotherapy fractionations. It is unlikely that all information on patient selection could ever be collected (11). However, given the reduced variability in fractionation in the UK, even if all necessary information on patient selection factors could be obtained in the future, it is unlikely that further observational studies could help to elucidate differences of effect between radiotherapy dose-fractionations of curative intent.

The implications of this cohort study are therefore to discourage reliance on observational data to study differences in radiotherapy dose-fractionation and instead to encourage new randomised trials.

3 Further research needed

3.1 New randomised trials

This thesis has shown that observational data are not appropriate for identifying differences in long-term outcomes due to differences in radiotherapy dose-fractionations. However, randomised trials that include a sufficiently large number of patients do have the potential to detect such differences. Both in NSCLC and in breast cancer, there may be scope for more randomised trials investigating the benefits of dose escalation via novel dose-fractionations. In the development of new trials, a time factor should be included in formulae comparing doses between trial arms.

In NSCLC, the optimal radiotherapy dose-fractionation is unknown. Despite negative results from the RTOG 0617 trial, there is still scope for further trials of radiotherapy dose-escalation (2). In such trials, modern radiotherapy techniques, for example intensity modulated radiotherapy (IMRT) or personalised isotoxic dose escalation, could help to minimise the effects on normal tissues of increasing tumour dose.

New randomised trials should report information on cause of death, numbers of events and numbers at risk in different periods of follow-up, hazard ratios of cancer-specific survival and overall survival in addition to median survival, and hazard ratios for side-effects, including ischaemic heart disease. They should also record information for each patient on doses to organs at risk as well as volume irradiated to enable more refined analyses of outcomes of different radiotherapy dose-fractionations. For example, reporting of information in the RTOG 0617 study is much more detailed than was the case in older trials (12).

In invasive breast cancer, the START trials have provided strong evidence in favour of giving 40 Gy in 15 fractions, rather than longer regimens formerly common in the UK. As a result of these trials, UK guidelines have changed from formerly suggesting several different regimens in 2006 to only recommending 40 Gy in 15 in 2016 (2, 10). In the United States, where conventional treatment in

≈2 Gy per fraction has had a much stronger tradition than in the UK, guidelines have also been shifting toward 40 Gy in 15 fractions for invasive breast cancer patients (13).

Even though the START trials have had a large impact on radiotherapy guidelines and practice, there may be scope for further research into different dose-fractionations in breast cancer. Depending on overall treatment time, the EQD2T for 40 Gy in 15 fractions is 44.4 Gy, while the EQD2T for 50 Gy in 25 fractions is 44.6 Gy. The two regimens are essentially the same biologically effective dose. Regimens being compared in two newer trials also have similar EQD2Ts. The FAST trial (14) compares 50 Gy in 25 (44.6 Gy EQD2T) with 30 Gy in 5 (46.8 Gy EQD2T) and with 28.5 Gy in 5 (42.9 Gy EQD2T), while the FAST-Forward trial (15) compares 40 Gy in 15 (44.4 Gy EQD2T) with 27 Gy in 5 (48.1 Gy EQD2T) and with 26 Gy in 5 (45.6 Gy EQD2T).

The main aim of the FAST and FAST-Forward trials is to reduce the number of fractions, but not to increase the dose delivered to the tumour. Delivering total dose in just five fractions has benefits for health systems as well as patients, as there is a lower burden on radiotherapy machines and staff, and patients need only to travel to hospital five rather than 15 or 25 times. However, as these newer regimens do not escalate dose, the benefits or risks of increasing EQD2T in the treatment of breast cancer are not being explored.

It is possible, however, that escalating dose in breast cancer is not a relevant question. Unlike in NSCLC, in which radiotherapy for locally advanced, inoperable patients is used to remove macroscopic disease, in breast cancer, radiotherapy is used to remove microscopic disease after the tumour has been surgically removed. Curative radiotherapy for breast cancer patients aims to reduce the risk of recurrence. However, the risk of recurrence is already low (16), so it is possible that the risks of increasing dose might outweigh any benefits. These risks and benefits would need to be studied in any future research.

3.2 Further work on meta-analyses of randomised trials

Meta-analyses of randomised trials may suffer from bias as data are not usually analysed at the individual patient level. However, combining data from multiple trials has the benefit of greater statistical power. This is especially important for cancer sites in which it is challenging to recruit sufficient numbers of patients to detect small differences of effect. An added benefit of meta-analyses is that differences between many dose-fractionations can be compared, rather than being limited to two or three dose-fractionations in a single trial. In invasive breast cancer, trials comparing radiotherapy dose-fractionations have mostly compared regimens with very similar EQD2Ts (see page 196). It would therefore be difficult to assess the effects of dose-escalation in a meta-analysis of existing trials in breast cancer. In other cancer sites, however, there may be a potential to explore the effects of different radiotherapy dose-fractionations in meta-analyses.

3.2.1 Individual patient data analysis using data from existing trials

Individual patient data analyses are much more difficult to conduct than meta-analyses making use of published data. Data must be obtained from the different studies, in order to combine them in analyses. This may take a lot of time to accomplish, and there may be many barriers to obtaining data. In the case of NSCLC, however, results of my meta-analysis have the potential to influence the development of future clinical trials. An individual patient data analysis including patients from 8/21 trials identified in this meta-analysis has already been published (17). It would be beneficial to add individual patient data from the other trials to that dataset, particularly from the Chinese trials, considering the striking differences in results by geographic region (Figure 2.5, Panel A).

An individual patient data analysis would ideally include information on patients' age, sex, smoking status, histopathology, stage, tumour location, type and dose of chemotherapy, and timing of chemotherapy relative to radiotherapy. Information would also be needed on time from randomisation to death or exit from follow-up, cause of death, and timing and type of

radiotherapy side-effects. Information on doses to normal tissues, especially to the heart, would also be useful. However, information on doses to normal tissues is not likely to have been recorded for patients in most trials included in this meta-analysis. Cardiac toxicity was reported in some form in only 4/21 trials (12, 18-20). Cardiac dose was only specifically alluded to in one trial (12), but it may be possible to derive if individual patient's treatment plans are still available. For example, cardiac radiotherapy dose and cardiac toxicity were successfully retrospectively assessed for 127 patients enrolled in six phase I/II clinical trials of radiotherapy and chemotherapy conducted between 1996 and 2009 (21).

With detailed individual patient data, it may be possible to conduct a survival analysis comparing higher versus lower dose within trial arm comparisons, subdivided according to whether concurrent, sequential, or no chemotherapy was given. If the underlying cause of death were available in an individual patient data analysis, it would be informative to study lung-cancer-specific survival, rather than overall survival.

It would also be informative to examine the effect of increasing EQD2T on radiotherapy side-effects, for example ischaemic heart disease. Jeffrey Bradley, primary author on the RTOG 0617 trial, commented on the meta-analysis in Chapter 2 that he believed radiotherapy dose to the heart in patients in the higher-dose arm was the reason patients who had received the higher dose had poorer survival in his trial (22). Information on dose to the heart, or at a minimum incidence of heart disease, for patients in these studies could shed light onto this hypothesis.

4 Summary of conclusions

1. Individual randomised trials of radiotherapy dose-fractionation in non-small cell lung cancer often have insufficient power individually to detect any effects of different fractionations. Combining the trials in a meta-analysis, however, permitted questions about radiotherapy dose-fractionation to be answered. In the future, an individual patient data analysis could help to minimise any confounding effects.
2. In 18 NSCLC trials that randomised patients to different radiotherapy dose-fractionations and in which no chemotherapy was given, radiotherapy dose escalation improved overall survival (median survival ratio: 1.13, 95% CI 1.04-1.22), corresponding to an average survival gain of approximately two months. The survival improvement increased progressively as the difference between EQD2T in the two trial arms increased. Even for trials in which the dose in the lower-dose arm was high (≥53.5 Gy EQD2T), further dose escalation provided additional improvement in survival. A threshold of dose above which patients no longer benefit does not yet appear to have been reached.
3. In trials with concurrent chemotherapy, higher EQD2T led to poorer overall survival, suggesting that risks of increasing radiotherapy dose outweigh benefits when concurrent chemotherapy is given (median survival ratio: 0.83, 95% CI 0.71-0.97). When chemotherapy is given with radiotherapy, the ability to achieve a cure has, until now, been limited by toxicity. However, in the context of new advances, such as personalised isotoxic radiotherapy dose escalation, and in the continued search for the optimal concurrent chemotherapy regimen, there is scope for further trials in radiation dose-escalation of chemoradiotherapy for locally advanced NSCLC.
4. Observational data were not suitable for studying long-term effects of different radiotherapy dose-fractionations. This is because there remain patient selection factors that differ by treatment centre, about which there was no information available in these data. The nature of these patient selection factors is such that it would be difficult to collect adequate information

to control for these in any future studies, particularly for the large number of patients required to study differences in radiotherapy dose-fractionation.

5. This thesis has demonstrated that it is possible to bring together English cancer registration and other data held within Public Health England to obtain a dataset containing wide-ranging information on many cancer patients. These data are now held in a single large electronic database, and their quality is likely to continue to improve in the years to come. There are likely to be many important questions that can be explored using these data.

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Appendix 1

Additional Material for Chapter 2

Supplementary Text 1: Terms used in Embase to search for eligible trials from 1 January 1974 to 28 April, 2015.

An initial search was conducted (A below). This search was updated (B below) using narrower search terms. A sensitivity analysis was conducted in the older search using the narrower search terms to ensure that the new search would include all articles of interest without excluding any. The original searches were conducted using the full Embase database, which starts 1 January, 1974. However, it was found that a substantial number of trials published prior to 1980 used old radiotherapy methods, such as Cobalt. It was therefore decided, prior to conducting any analyses, only to include trials starting in 1980 or later.

A. In search conducted up to 12 September, 2013:

1. exp radiation dose fractionation/
2. fraction*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. (hypofraction* or hyperfraction*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4. "accelerat* radiotherap*".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. (radiotherapy adj5 (regimen* or schedule*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. human/
7. letter/
8. editorial/
9. phase 1 clinical trial/
10. 7 or 8 or 9
11. exp *lung cancer/ or exp *lung tumor/ or exp *lung carcinoma/
12. exp *pleura cancer/ or exp *pleura tumor/
13. exp *bronchus cancer/ or exp *bronchus tumor/
14. (bronch* adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).m_titl.
15. (lung adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).m_titl.
16. (pleura* adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).m_titl.

17. 11 or 12 or 13 or 14 or 15 or 16

18. 1 or 2 or 3 or 4 or 5

19. 6 and 17 and 18

20. 19 not 9

B. In search update from 12 September, 2013 to April 28, 2015:

1. exp radiation dose fractionation/

2. fraction*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

3. (hypofraction* or hyperfraction*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

4. "accelerat* radiotherap*".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

5. human/

6. letter/

7. editorial/

8. phase 1 clinical trial/

9. 6 or 7 or 8

10. exp *lung cancer/ or exp *lung tumor/ or exp *lung carcinoma/

11. exp *pleura cancer/ or exp *pleura tumor/

12. exp *bronchus cancer/ or exp *bronchus tumor/

13. (bronch* adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

14. (lung adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

15. (pleura* adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

16. 10 or 11 or 12 or 13 or 14 or 15

17. (bronch* adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).m_titl.

18. (lung adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).m_titl.

19. (pleura* adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).m_titl.

20. 10 or 11 or 12 or 17 or 18 or 19

21. (radiotherapy adj5 (regimen* or schedule*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

22. 1 or 2 or 3 or 4 or 21

23. 5 and 16 and 22

24. 23 not 9

25. 5 and 20 and 22

26. 25 not 9

27. "accelerat* adj3 radiotherap*".mp.

28. (accelerat* adj3 radiotherap*).mp.

29. 1 or 2 or 3 or 28 or 21

30. 5 and 20 and 29

31. 30 not 9

32. exp radiation dose fractionation/

33. fraction*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

34. (hypofraction* or hyperfraction*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

35. "accelerat* radiotherap*".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

36. human/

37. letter/

38. editorial/

39. phase 1 clinical trial/

40. 37 or 38 or 39

41. exp *lung cancer/ or exp *lung tumor/ or exp *lung carcinoma/

42. exp *pleura cancer/ or exp *pleura tumor/

43. exp *bronchus cancer/ or exp *bronchus tumor/

44. (bronch* adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

45. (lung adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

46. (pleura* adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

47. 41 or 42 or 43 or 44 or 45 or 46

48. (bronch* adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).m_titl.

49. (lung adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).m_titl.

50. (pleura* adj5 (neoplas* or carcinom* or cancer* or tumor* or tumour*)).m_titl.

51. 41 or 42 or 43 or 48 or 49 or 50

52. (radiotherapy adj5 (regimen* or schedule*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

53. 32 or 33 or 34 or 35 or 52

54. 36 and 47 and 53

55. 54 not 40

56. 36 and 51 and 53

57. 56 not 40

58. "accelerat* adj3 radiotherap*".mp.

59. (accelerat* adj3 radiotherap*).mp.

60. 32 or 33 or 34 or 59 or 52

61. 36 and 51 and 60

62. 61 not 40

63. 62

64. limit 63 to yr="2013 -Current"

65. (kinase or centrifugal or retinoic or ascorbate or antigen or c-myc or keratin or gefitinib or telomerase or "in vitro" or "cytometry" or "cytometric" or p53 or p50 or p54 or p73 or p63 or HtrA3 or KRAS or K-RAS or thyrosinase or allele or LLC1).m_titl.

66. 64 not 65

67. (lipid or plasminogen or proteolysis or mutation or biogenesis or heterozygosity or monoclonal or apoptosome or kinetic or inhibitor or tenascin or isoenzyme or enzyme or CDKN2 Phenethyl or immunoreactivity or epigenetic or methylation or entropy).m_titl.

68. (beta-carotene or retinoid or annexin or herbal or proteomics or centrosome or monoclonal or clonal or "effector cell" or immunostaining or lectin or lymphokine or Dendritic or immunotherapy or macrophage or RNA or receptor or "cell line" or "cell lines" or xenograft).m_titl.

69. 65 or 67 or 68

70. 64 not 69

71. small cell lung cancer/ or lung small cell cancer/

72. 70 not 71

73. brain metastasis/ or skull irradiation/

74. 72 not 73

75. ("prophylactic cranial irradiation" or PCI).m_titl.

76. 74 not 75

77. patient*.ab.

78. 76 and 77

79. random*.ab.

80. 78 and 79

Supplementary Text 2: Additional methodological details

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines specify that a systematic review should consider possible risks of bias, both within studies and between them (1). To this end, we provide details regarding trial identification, the outcome measure, small study effects, and heterogeneity between trials. We also provide some other methodological details.

Method of trial identification

The search criteria were reviewed by two authors (CT and SD) and a librarian. Abstracts were screened by one author (JR) and included trials were reviewed by three (JR, CT, and SD). Decisions on the inclusion of trials of SCLC versus NSCLC, palliative versus curative intent radiotherapy, cut-off year (1980), methods of randomisation, and language were made by JR, CT, and SD. Trials for which methods of randomization were not indicated in the publication were included, but one trial stating the use of hospital numbers to randomize was excluded (2). Eligible trials for which publications were not in English (German, French, and Chinese) were translated and included, and three further articles (Russian and Japanese) were reviewed and deemed ineligible. We successfully contacted authors of three Chinese articles in order to obtain manuscripts not otherwise available. We contacted authors of a Polish study for which only an abstract was available, and obtained information about numbers of deaths and median survival in each trial arm.

Outcome measure

Median survival was selected as our outcome measure as it has good statistical properties (3) and it was the measure most frequently available in eligible trials. Five trials (study numbers 1, 8, 16, 17, 18) did not provide information on median survival and had no Kaplan-Meier plot, so median survival time was estimated from 1-year survival assuming that the survival times had an exponential distribution. In the three trials in which median survival had to be read from plots (study numbers 5, 7, 15), these were magnified and a ruler was used.

The standard error (SE) for the log of the median survival ratio in each trial was estimated as follows:

$$SE_{log\_median\_survival\_ratio} = \sqrt{\frac{1}{D_1} + \frac{1}{D_2}},$$

where D_1 is the number of patients who died in arm 1 and D_2 the number who died in arm 2 (4).

The number of patients who had died in each study arm was obtained as follows in the 21 trials: in four trials, the numbers were stated in the text and in one it was obtained via personal communication from study investigators. In one further study, the numbers were estimated from median survival time or median follow-up time; and in the remaining 15 studies, numbers died were estimated from the Kaplan Meier plot or the proportion surviving at the longest reported period (eg. at 3 or 5 years). If numbers were estimated from a Kaplan Meier plot, the proportion died was assumed to be the proportion not surviving with no censoring due to loss to follow-up.

Use of the median survival could lead to some dilution of effect, as some patients with unidentified metastatic disease at the outset may still be alive at the median survival point, whereas most of these patients would have died by a later point, for example at two years. Unfortunately, two-year survival could not be used, because obtaining a standard error for two-year survival was not possible, as rates of death in each trial arm were not available.

Statistical analyses

We used fixed-effects meta-analysis. Three types of statistical test formed the basis of results presented in forest plots. Within-group heterogeneity was calculated in order to assess whether variability between studies was greater than due to the play of chance. Between-group heterogeneity was assessed in order to determine whether subgroups were statistically different from one another. In order to assess trends, either across studies ordered within a group, or between ordered groups, chi-squared tests for trend were conducted.

The test for heterogeneity we used in the various meta-analyses was a weighted chi-squared test (Cochran's Q chi-squared test statistic) as follows:

$$Q = \sum_i \left[\left(\frac{1}{v_i}\right) * \left(\text{Effect}_i - \text{Effect}_{\text{pooled}}\right)^2\right],$$

where Q is distributed on N-1 degrees of freedom, Effect_i is the log median survival ratio of a given study, $\text{Effect}_{\text{pooled}}$ is the overall pooled log median survival ratio, and v_i is the variance of the log median survival ratio of a given study (the square of the standard error given above).

Small study effects

A funnel plot was generated in order to assess whether there may be small study effects, including publication bias (Fig. E4). Funnel plots scatter study effects by size of the study, such that bigger studies' effect sizes should be closer to the overall effect size, while smaller studies will vary more. However, regardless of study size, their effects should scatter symmetrically about the overall effect determined in the meta-analysis (5). Small studies are sometimes less likely to be published than big studies if they do not show a statistically significant effect. There may also be systematic reasons why smaller studies show bigger effects (5). Either way, small study effects are more prone to result in asymmetry around the effect line. In our meta-analysis, however, there was no visible asymmetry among the smaller trials (Fig. E4). Egger's test of no linear association between the treatment effect and its standard error was performed in order to assess asymmetry in the plot (p=0.3) (6).

Sources of heterogeneity

There was evidence of significant heterogeneity between trials in the median survival ratios, higher versus lower radiotherapy dose (Fig. 2). This heterogeneity is visible in the funnel plot described above (Fig. E4), as more than the expected 5% of trials lie outside the diagonal funnel lines (4/18 trials). The degree of heterogeneity between trials of radiotherapy without chemotherapy (χ^2=45.8 on 17 degrees of freedom, p<0.001) prompted us to conduct further analyses, both of heterogeneity due to the variation in EQD2T dose differences between trial arms (Fig. E2) and by potential confounding factors (main article). The EQD2T dose difference between trial arms ranged from 1.1 Gy to 27.2 Gy and the proportion of excess heterogeneity between studies due to dose differences in trial arms was calculated to be 28.7%, leaving over two-thirds unaccounted for. The potential confounding factors were only available at the aggregate level and thus their effects on heterogeneity could not be examined in detail (Discussion). There may also be other factors not as widely reported in the trials that could also contribute to the heterogeneity between trials.

Categorization of chemotherapy

In this study, chemotherapy was divided into two categories, concurrent and sequential. Trials defined as giving concurrent chemotherapy were those in which chemotherapy was given on the same day as any radiotherapy fraction (N=4). Of the four trials defined as giving concurrent chemotherapy, two also gave consolidation chemotherapy i.e. chemotherapy after the end of radiotherapy. Two trials were defined as giving sequential chemotherapy (N=2). In one of these trials (number 9), chemotherapy was given before radiotherapy, and there was a minimum gap of

eleven days between the end of chemotherapy and the start of radiotherapy. In the other sequential trial (number 20), chemotherapy was given both before and after radiotherapy, but the number of days between chemotherapy and radiotherapy treatment was not specified. As there were so few trials giving chemotherapy (six in total), further subdivisions of chemotherapy (whether by type or timing) were not possible due to statistical power constraints.

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Table 1. Trials included in meta-analysis, ordered according to EQD2T* radiotherapy dose difference between trial arms: patient characteristics, outcomes and any excluded trial arms

Trial no.†	Author, year (ref)	Randomisation years	Country	No. patients	Age (years)	Percent male	Stage: System used, percent in each group	Percent SCC	Trial arm ‡	Median survival in trial arm (months)	Median survival ratio, higher to lower dose	Excluded trial arms
1	Zhan 2007 (35)	2000 - 2005	China	159	Mean: 59	75	IIIA§ : 42% IIIB: 58%	38	A B C	16.4 15.4 17.6	0.9 0.9 baseline	In three included arms patients received the same chemotherapy; in a fourth excluded arm, patients received radiotherapy only
2	Saunders 1999 (19)	1990 - 1995	UK, Germany, Sweden	563	31-50: 7% 51-60: 24% 61-70: 43% 71+: 26%	77	IA§ : 6% IB: 24% II: 7% IIIA: 38% IIIB: 23% Unknown: 3%	82	A B	16.5 13.0	1.3	-
3	Schild 2002 (20)	1994 - 1999	US	234	NS	62	IIIA§ : 52% IIIB: 48%	37	A B	14.0 15.0	0.9	-
4	Bonner 1998 (21)	1992 - 1993	US	67	Median: 64	63	IIIA§ : 60% IIIB: 40%	63	A B	8.2 11.6	0.7	In two included arms patients received radiotherapy only; in a third excluded arm, patients also received chemotherapy
5	Cox 1990 (22)	1983-1987	US	516	<60: 36% 60-70: 44% >70: 19%	76	RTOG ¦ II: 12% III: 55% IV: 33%	54	A B C D E	10.5 8.7 10.0 6.3 9.2	1.1 0.9 1.1 0.7 baseline	-
6	Slawson 1988 (23)	1982 - 1986	US	120	NS	NS	AJCC 1977 ¶ III: 97% IV: 3%	69	A B	10.0 12.0	0.8	-
7	Baumann 2011 (17)	1997 - 2005	Germany, Poland, Czech Republic	406	Median: 66 (range 38 - 87)	90	UICC 1992 I: 10% II: 6% IIIA: 38% IIIB: 46% Unknown: 0%	58	A B	15.6 15.6	1.0	-
8	Fu 1994 (24)	1990 - 1992	China	105	Median: 61 (range 21-78)	86	UICC 1989 I + II: 11% IIIA: 55% IIIB: 35%	64	A B	13.1 7.3	1.8	-
9	Belani 2005 (25)	1998 - 2001	US	119	Median: 65 (range 40-77)	61	Stages IIIA, IIIB § #	42	A B	20.3 14.9	1.4	-
10	Sapkota 2013 (26)	NS	India, Nepal	30	NS	NS	Unresectable but not metastatic **	NS	A B	18.0 15.0	1.2	-
11	Sause 2000 (27)	1989 - 1992	US, Canada	301	NS	70	AJCC 1988 II: 6% IIIA: 45% IIIB: 49%	44	A B	12.0 11.4	1.1	In two included arms patients received radiotherapy only; in third excluded arm, patients also received chemotherapy
12	Reinfuss 1999 (28)	1992 - 1996	Poland	160	<50: 14% 50-60: 43% >60: 43%	89	UICC 1987 IIIA: 34% IIIB: 66%	90	A B	12.0 9.0	1.3	One arm excluded as patients received no radiotherapy
13	Zajusz 2006 (32)	2001 - 2006	Poland	53	Mean: 62	NS	Stages II-III § **	NS	A B	13.7 14.1	1.0	-
14	Bradley 2015 (6)	2007 - 2011	US, Canada	424	Median: 64	59	AJCC ¦ IIIA: 65% IIIB: 35%	44	A B	20.3 28.7	0.7	-
15	Ball 1999 (18)	1989 - 1995	Australia	99	Median: ~65 (range 40-79)	77	UICC 1987 I: 18% II: 4% IIIA: 49% IIIB: 28% IV: 1%	85	A B	14.4 13.8	1.0	In two included arms patients received radiotherapy only, in two excluded arms, patients also received chemotherapy but differing regimens
16	Zhu 2000 (36)	1993 - 1996	China	70	Median: 48	87	UICC 1989 Inoperable I, II, IIIA. or IIIB **	60	A B	32.0 16.3	2.0	-
17	Cheng W 2007 (34)	1999 - 2002	China	81	Mean: 60	74	UICC 1997 IIIA: 51% IIIB: 49%	47	A B	30.6 13.4	2.3	-
18	Cheng J 2004 (33)	1995 - 1998	China	74	Median: 54	78	UICC 1992 IIIA: 78% IIIB: 22%	71	A B	29.9 17.5	1.7	-
19	Wang 2005 (29)	2001 - 2003	China	86	Median: 48	66	UICC 1997 IIIA: 45% IIIB: 55%	41	A B	19.8 11.4	1.7	-
20	Yu 2014 (31)	2009 - 2011	China	60	Median: 64 (range 36-74)	78	AJCC 2007 IIIA: 52% IIIB: 48%	65	A B	20.5 17.8	1.2	-
21	Wang 2008 (30)	2004 - 2006	China	68	Median: ~50	68	UICC 1997 IIIA: 41% IIIB: 59%	37	A B	18.3 12.6	1.5	-

Abbreviations : SCC = squamous cell carcinoma; NS = not specified. RTOG = Radiation Therapy Oncology Group. AJCC = American Joint Committee on Cancer. UICC = Union for International Cancer Control.

* EQD2T is time-corrected equivalent dose in 2 Gy fractions.

† Trials numbered according to ascending dose difference between trial arms

‡ Study arms presented in order of descending difference in EQD2T between trial arms

§ No staging system provided

¦ No year of staging system provided

¶ AJCC 1977 staging used with an RTOG modification for Stage IV

Patients eligible if stages IIIA and IIIB. Percent of patients by stage only given for T and N separately.

** Percent of patients by stage not specified

Table 2. Trials included in meta-analysis, ordered according to EQD2T* radiotherapy dose difference between trial arms: protocol treatment information, radiotherapy and chemotherapy

		Radiotherapy dose/fractionation							EQD2T*		Chemotherapy
Trial no.†	Author, year (ref)	Trial arm‡	Total dose (Gy)	Dose per fraction (Gy)	No. fractions	No. fractions per day/ days of RT per week	Split course RT: length of break	Average total treatment time (days) §	EQD2T* (Gy)	EQD2T difference between arms (Gy)	Protocol treatment
1	Zhan 2007 (35)	A	65.0 - 70.0	1.6	~42 ¦	2/5	A: 10 days	38.6	56.2	2.4	During and after RT: two cycles each cisplatin and etoposide.
		B	65.0 - 70.0	2.0	~56 ¦	2/5		47.2	54.9	1.1	
		C	65.0 - 70.0	1.2	~34 ¦	1/5		38.8	53.8	baseline	
2	Saunders 1999 (19)	A	54.0	1.5	36	3/7	-	12.0	51.8	2.1	-
		B	60.0	2.0	30	1/5		41.6	49.7		
3	Schild 2002 (20)	A	60.0	2.0	30	1/5		41.6	49.7	2.5	During RT: Etoposide 100mg/m², cisplatin 39mg/m²
		B	60.0	1.5	40	2/5	B: 2 weeks	41.6	47.2		
4	Bonner 1998 (21)	A	60.0	2.0	30	1/5		41.6	49.7	2.5	-
		B	60.0	1.5	40	2/5	B: 2 weeks	41.6	47.2		
5	Cox 1990 (22)	A	79.2	1.2	66	2/5		45.8	61.5	12.3	-
		B	74.4	1.2	62	2/5		43.0	58.4	9.2	
		C	69.6	1.2	58	2/5	-	40.2	55.4	6.2	
		D	64.8	1.2	54	2/5		37.4	52.3	3.1	
		E	60.0	1.2	50	2/5		34.6	49.2	baseline	
6	Slawson 1988 (23)	A	60.0	2.0	30	1/5	-	78.0	49.7	3.2	-
		B	60.0	5.0	12	1/1		41.6	46.5		
7	Baumann 2011 (17)	A	60.0	1.5	40	3/5	-	19.2	57.5	3.9	-
		B	66.0	2.0	33	1/5		45.8	53.6		
8	Fu 1994 (24)	A	69.6	1.2-1.3	56-62	2/5	-	45.8	52.3	4.0	-
		B	63.9	1.8-2.0	32-26	1/5		50.0	48.3		
9	Belani 2005 (25)	A	57.6	1.5 - 1.8 ¶	36	3/5	-	17.8	55.7	4.1	Before RT: Carboplatin, area under the time-concentration curve 6 mg/mL/min; paclitaxel, 225 mg/m²
		B	64.0	2.0	32	1/5		45.8	51.6		
10	Sapkota 2013 (26)	A	60.0	1.5	40	2/5	-	27.6	54.2	4.5	During RT: Cisplatin weekly 30mg/m²
		B	60.0	2.0	30	1/5		41.6	49.7		
11	Sause 2000 (27)	A	69.6	1.2	58	2/5	-	40.2	55.4	5.7	-
		B	60.0	2.0	30	1/5		41.6	49.7		
12	Reinfuss 1999 (28)	A	50.0	2.0	25	1/5		34.6	43.2	6.8	-
		B	40.0	4.0	10	1/5	B: 4 weeks	41.6	36.4		
13	Zajusz 2006 (32)	A	72.0	1.8	40	1/7	-	40	61.3	7.8	-
		B	72.0	1.8	40	1/5		55.6	53.5		
14	Bradley 2015 (6)	A	74.0	2.0	37	1/5	-	51.4	58.8	9.1	Half of patients in arms A and B: Sequential and concurrent: weekly paclitaxel (45mg/m^2) and carboplatin (area under the time-concentration curve 2); Other half of patients in arms A and B: Sequential and concurrent: cetuximab; weekly paclitaxel (45mg/m^2) and carboplatin (area under the time-concentration curve 2)
		B	60.0	2.0	30	1/5		41.6	49.7		
15	Ball 1999 (18)	A	60.0	2.0	30	2/5	-	20.6	60.0	10.3	-
		B	60.0	2.0	30	1/5		41.6	49.7		
16	Zhu 2000 (36)	A	76.0	1.8 - 2.0 #	40	first 20: 1/5 #	-	55.6	68.8	12.6	-
		B	70.0	2.0	35	1/5		48.6	56.2		
17	Cheng W 2007 (34)	A	70.0	1.5 - 2.0 **	40	first 20: 1/5 **	-	41.6	68.8	12.6	-
		B	68.0 - 72.0	2.0	34 - 36	1/5		48.6	56.2		
18	Cheng J 2004 (33)	A	64.0	1.2 - 2.0 ††	40	first 20: 1/5††	-	41.6	68.8	13.2	-
		B	65.0 - 70.0	2.0	33 - 35	1/5		45.8	55.6		
19	Wang 2005 (29)	A	64.0 - 70.0	2.0 - 5.0 ‡‡	26	first 20: 1/5 ‡‡	-	40.4	68.8	15.2	-
		B	66.0 - 70.0	2.0	33-35	1/5		45.8	53.6		
20	Yu 2014 (31)	A	65.0	2.5 - 3.0	25	1/5	-	34.6	68.8	15.6	Before and after RT: vinorelbine 25mg/m^2 and cisplatin 40mg/m^2
		B	60.0	2.0	30	1/5		34.6	53.2		
21	Wang 2008 (30)	A	80.0	2.0 - 5.0 §§	34	first 30: 1/5 §§	-	50.4	80.8	27.2	-
		B	66.0 - 70.0	2.0	33-35	1/5		45.8	53.6		

Abbreviations : RT = radiotherapy.

* EQD2T = time-corrected equivalent dose in 2 Gy fractions.

† Trials numbered according to ascending dose difference between trial arms

‡ Trial arms presented in order of descending difference in EQD2T between trial arms

§ Calculated as an average of the total days of treatment, assuming equal numbers of patients started regimen on each of five days (Monday to Friday)

¦ Number of fractions not indicated, so number of fractions estimated by dividing total dose by total treatment time

¶ The first and third fractions of each day were 1.5 Gy, the second fraction was 1.8 Gy

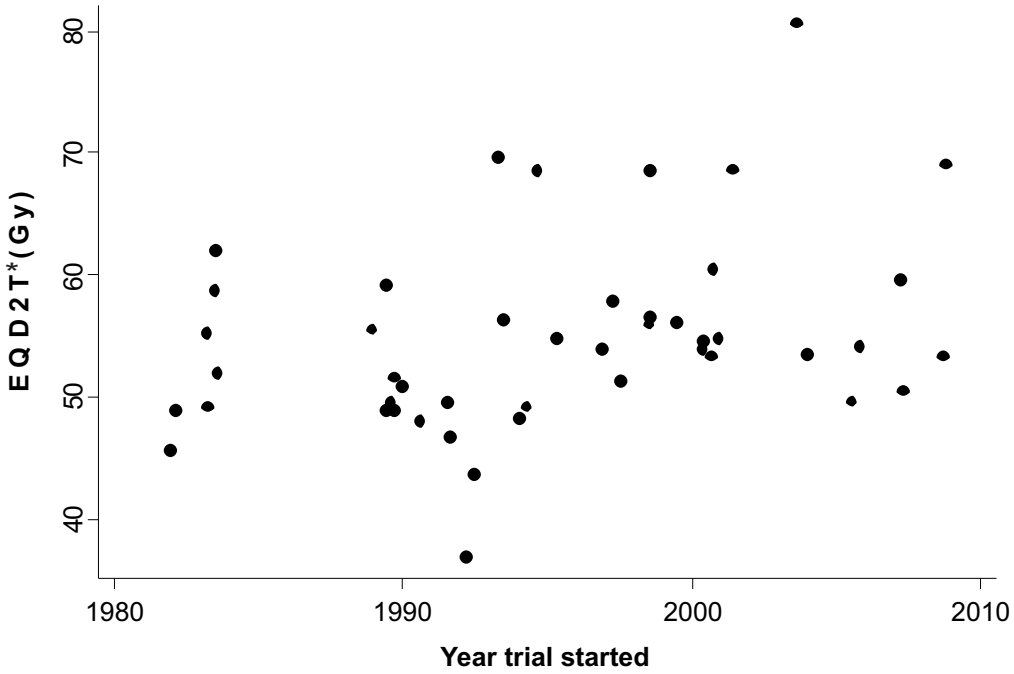
First 20 fractions conventional irradiation at 2 Gy per fraction, final 20 fractions delivered twice daily at 1.8 Gy per fraction

** First 20 fractions conventional irradiation at 2 Gy per fraction, final 20 fractions delivered twice daily at 1.5 Gy per fraction

†† First 20 fractions conventional irradiation at 2 Gy per fraction, final 20 fractions delivered twice daily at 1.2 Gy per fraction

‡‡ First 20 fractions conventional irradiation at 2 Gy per fraction, final six fractions at 4-5 Gy per fraction, final six fractions given every other day

§§ First 30 fractions conventional irradiation at 2 Gy per fraction, final four stereotactic fractions at 5Gy per fraction, final four fractions given every other day



* EQD2T is time-corrected equivalent dose in 2 Gy fractions
†Average increase in EQD2T per year: 0.31Gy (95% CI 0.02 - 0.61 Gy, p=0.04)

Figure 1. EQD2T* radiotherapy dose in individual arms of trials comparing different radiotherapy regimens, with or without chemotherapy, by year trial started†

Table 3. Correlation of geographical region, average age at trial entry, year trial started, and percent of patients with squamous cell carcinoma *

	Average age at trial entry	Geographical region	Year trial started	Percent with squamous cell cancer
Average age at trial entry	1.00			
Geographical region	0.69	1.00		
Year trial started	-0.71	-0.70	1.00	
Percent with squamous cell cancer	0.23	0.46	-0.45	1.00

* Trial number 13 is excluded from this analysis as it is missing information on histological subtype

Table 4. Variation in pooled median survival ratio, higher versus lower EQD2T dose, by average age at trial entry, geographical region, year trial started, and percent of patients with squamous cell carcinoma *

Exploratory factor	Group	Ratio † (95% CI)	p for heterogeneity
Average age at trial entry	≤60 60+ Average age in trial not known	1 0.87 (0.65 - 1.17) 0.76 (0.50 - 1.16)	0.4
Geographical region	China Elsewhere	1 0.66 (0.49 - 0.90)	0.008
Year trial started	1980s 1990s 2000s	1 1.13 (0.92 - 1.39) 0.78 (0.42 - 1.45)	0.2
Percent of patients with squamous cell carcinoma	<50% ≥50%	1 0.81 (0.59 - 1.12)	0.2

* Trial number 13 is excluded from this analysis as it is missing information on histological subtype.

† Ratio of pooled estimate of median survival ratio within each exploratory factor. If there is no effect, the ratio is equal to 1. Pooled median survival ratios were estimated by variance-weighted least squares. The results for each factor are shown after adjustment for the other three.

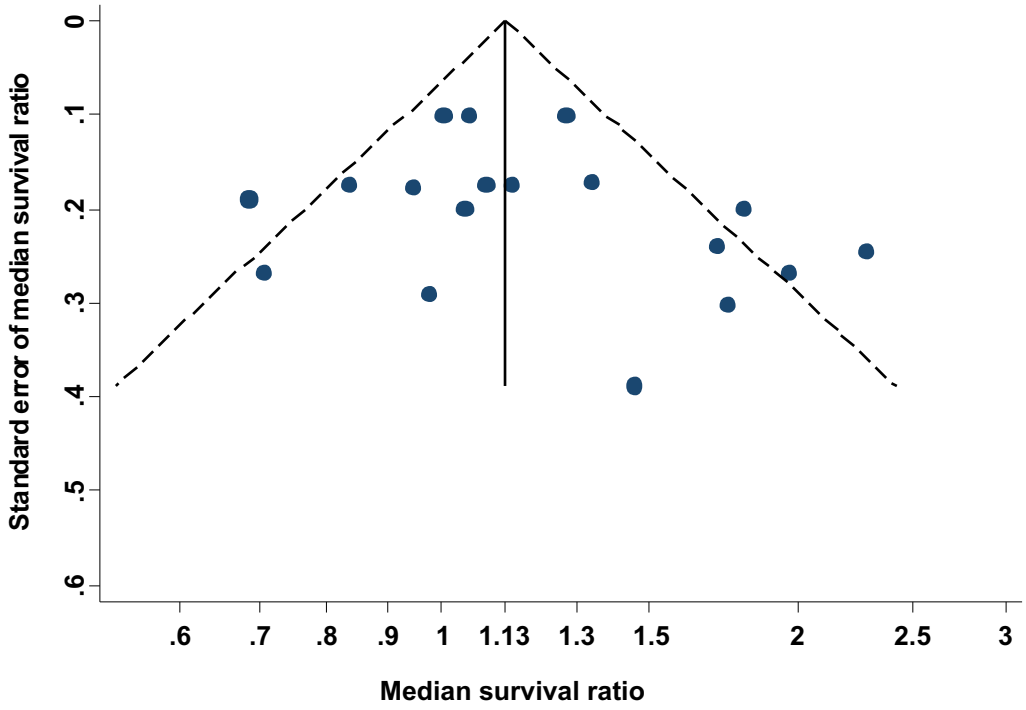


Figure 2. Funnel plot of median survival ratios and standard errors of randomised treatment comparisons in which radiotherapy is given without chemotherapy

Each point on this plot represents the standard error of the median survival ratio for a randomised dose comparison, plotted against the median survival ratio. The vertical solid line represents the pooled estimate of all randomised comparisons. The diagonal, broken lines represent the area around the line within which 95% of studies with the standard error indicated on the y-axis are expected to fall, given random variation only. The bigger the trial the closer to the top of the funnel it lies and the smaller the expected difference between its median survival ratio and the pooled effect. Small study effects are assessed by the degree of asymmetry in the points to the right or left of the line toward the bottom of the plot. If there were a high degree of asymmetry, there would be many points located in the bottom right or bottom left of the plot. In this study that is not the case. However, there are four studies (22%) that lie outside of the funnel (one to the left, three to the right), while only 5% (1 study) is expected to lie outside the plot if the only variation present was random. This shows that there is heterogeneity between the studies.

Appendix 2

Additional Material for Chapter 3

Supplementary Text 1: Cohort Study Protocol

Study Title: **Retrospective Analysis of the Effects of Different Radiotherapy Fractionation Schedules and of Differences in Blood Test Results on Outcomes in Cancer Patients**

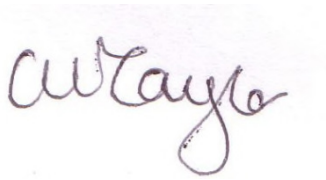
Internal Reference No/Short title: Retrospective Analysis of Radiotherapy Treatment Outcomes

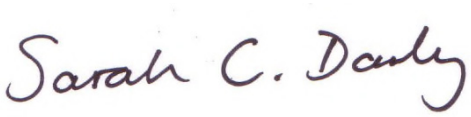
Ethics Ref: 13/SC/0610

Date and Version No: May 23, 2014, Version 2

Chief Investigator:	Dr. Carolyn Taylor
Investigators:	Professor Sarah Darby and Miss Johanna Rankin
Data Controller:	Heather House
Institute	University of Oxford / ORH NHS Trust
Location of Database	
Funder:	Cancer Research UK

Signatures:





Dr. Carolyn Taylor Professor Sarah Darby

The study investigators and collaborators declare no conflicts of interest.

TABLE OF CONTENTS

1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
	1	2013/07/05	NA	

2. SYNOPSIS

This study by the University of Oxford will be a retrospective analysis of radiotherapy outcomes in cancer patients. The study will explore to what degree the efficacy of radiotherapy and the risk of side-effects depend on the dose of radiation received by the patient and the number of fractions in which the dose is delivered. In addition, it will examine whether the efficacy of radiotherapy is associated with various blood measurements before treatment begins. The data to be used in this study will be obtained from the National Cancer Registration Service and from participating hospitals by the Knowledge and Intelligence Team (South East). Data items will include radiotherapy dose and fractionation, other cancer treatments, cancer diagnosis and characteristics, comorbidities, patient characteristics, blood test results, cancer recurrence or second cancers, and death. A fully linked and anonymised datafile will be transferred to the University of Oxford for analysis.

The study is funded by Cancer Research UK and the Clinical Trial Service Unit at the University of Oxford. The first phase of the study is scheduled to last for three years and it is planned that a broader study will then be performed. Patients in the study will not be contacted, as the data was collected in the past. The study results will be of relevance to oncologists, to cancer patients, and to members of the general public, who may need treatment for cancer in the future.

Research Database Title	Radiotherapy Treatment Outcomes
Internal ref. no.	
Collection methods	Pre-existing and ongoing routine data collection
Types of Data Collected	Cancer registry, biochemistry, haematology, radiology, pathology, chemotherapy
Number of Participants from which data will be collected	~25,000 in the first instance.
Planned Approval Period	November 2013

Primary Objective	The primary objective is to ascertain which radiotherapy fractionation schedules, including the total dose and the number of fractions in which the dose is delivered, are better than others at curing cancer in terms of reducing the rate of recurrence of the cancer and of cancer-related death.
Secondary Objectives	The secondary objectives to be addressed are: - to ascertain which radiotherapy fractionation schedules are better in terms of the risk of side-effects. - to ascertain whether the efficacy of radiotherapy depends on the levels of various blood measurements before treatment begins.

3. ABBREVIATIONS

NHS	National Health Service
KIT	Knowledge and Intelligence Team (Cancer Registration Service)
DPhil	Doctor of Philosophy
UK	United Kingdom
PSA	Prostate specific antigen

4. BACKGROUND AND RATIONALE

Note: On 1st April, 2003, the regional registries across England became part of Public Health England, an executive agency of the Department of Health. Regional registry teams are now called Knowledge Intelligence Teams (Oxford being denoted as "South East" and Trent being denoted as "East Midlands"). When these teams have conducted work in the past, the former regional registry names are used, while for any current or future actions their new names are used. Knowledge and Intelligence Team is abbreviated to "KIT".

Background

Radiotherapy is widely used to treat cancer. However, it is not always effective in curing the disease and, even when it is effective, it may have serious side-effects (1-4). It is likely that both the efficacy of radiotherapy and the risk of side-effects depend on the radiotherapy fractionation schedule, that is the total dose of radiation to the target tissue and the number of sessions, or fractions, in which it is delivered. The efficacy of radiotherapy may also be associated with various blood measurements before radiotherapy begins.

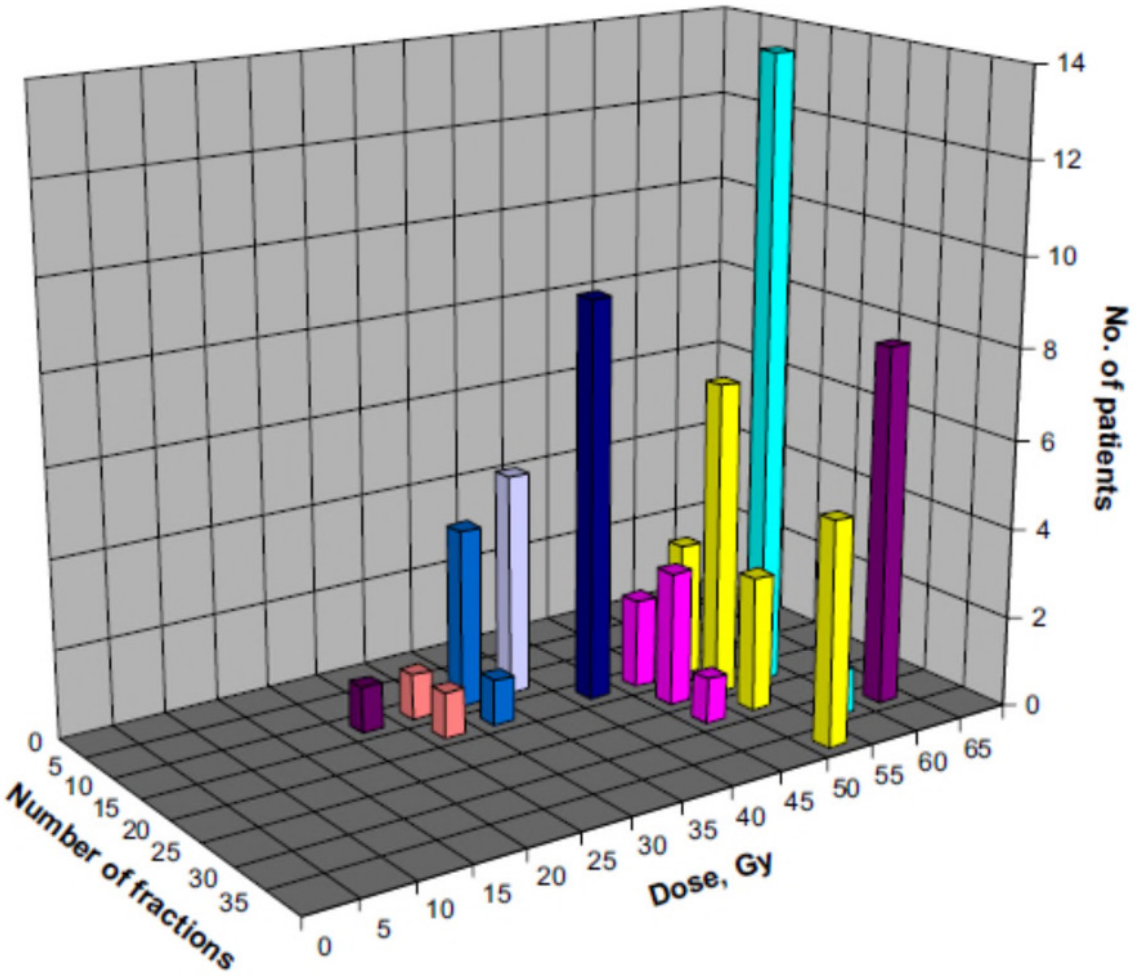


Figure 1: Three-dimensional plot of the number of patients treated using different radiotherapy fractionation schedules in the National Survey of Radiotherapy Fraction Practice in 2003, for radical treatment of lung cancer(5).

In order to study associations between cancer outcome and either the radiotherapy fractionation schedule or initial blood test results, follow-up data are needed on a large number of patients with sufficient variability in the radiotherapy schedule and in the blood measurements prior to radiotherapy to detect effects reliably.

Radiotherapy in the UK

The UK provides an excellent environment to conduct this study, as radiotherapy fractionation schedules have been less uniform over the past few decades than elsewhere internationally (6). A survey in 1989 asked UK Clinical Oncologists about the radiotherapy fractionation schedule they

would prescribe in six hypothetical patient scenarios: two curative, two palliative, and two in which "the role of irradiation is less well defined" (7). The authors found that most consultants used different fractionation schedules for each of the six scenarios. The schedules used involved a range of 6 to 45 fractions in curative situations and 1 to 36 fractions in palliative ones.

Another study, conducted by the Royal College of Radiologists in 2003, examined dose and fractionation in a one-week audit of all radiotherapy treatments in the UK. It found that, although

radiotherapy schedules were more consistent than they had been in 1989, they were still far from uniform. For example, radical treatment of lung cancer saw 13 patients who were treated with 55 Gy in 20 fractions, eight patients with 40 Gy in 15 fractions, eight patients treated with 60 Gy in 30 fractions, six patients treated with 50 Gy in 20 fractions, and twelve other combinations for smaller numbers of patients – see Figure 1 (5). In a third study, carried out by the former Oxford Cancer Intelligence Unit, it was found that the four main radiotherapy centres serving the Thames Valley area during the period 1999 to 2010 used a wide variety of fractionation regimens for radical breast cancer treatment – see Figure 2 (8).

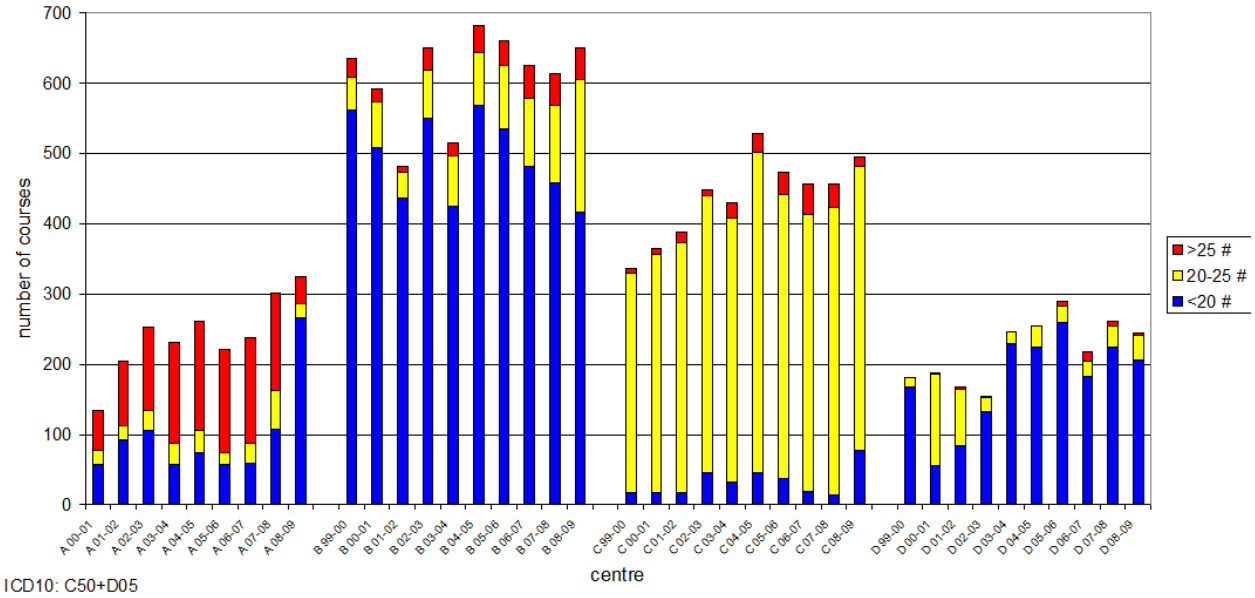


Figure 2: Trends in breast cancer radical radiotherapy fractionation schedules by calendar year for four centres in the Thames Valley area. Centres denoted by A, B,C,D. Calendar years by 99-01, 00-01, ..., 08-09. Schedules are blue: <20 fractions, yellow: 20-25 fractions, red: >25 fractions.(8).

Findings on the diversity of radiotherapy dose-fractionation schedules led to the Royal College of Radiologists' publication "Radiotherapy Dose-Fractionation" in 2006. In this report, the evidence base of radiotherapy fractionation schedules was reviewed and graded.

Radiotherapy was reviewed separately for radical and palliative intent (6). This initiative was concurrent with efforts to standardize radiotherapy practice, including the National Institute for Health and Clinical Excellence guidelines (9) and the National Radiotherapy Advisory Group model of radiotherapy demand (10-12). However, in 2012, although dose and fractionation had become more uniform for breast radiotherapy in the UK (as compared with UK surveys in 1993 (13) and 2003 (5)), radiotherapy practices still remained highly variable for prostate, lung, and head and neck cancers (14). The Royal College report concluded that further studies, especially observational studies of the type proposed here, should be carried out, in order to improve understanding of the effects of variation in radiotherapy dose and fractionation.

A systematic review of publications reporting outcomes after different curative-intent radiotherapy fractionation schedules is underway. Preliminary findings suggest that for most cancer sites, evidence consists of small randomised trials comparing two or sometimes three different

fractionation schedules in a select group of patients. The exceptions are breast cancer and head and neck cancer, for which a number of larger trials have been conducted.

5. OBJECTIVES

We plan to carry out a long-term follow-up study using data from patients who have been treated with radiotherapy in the UK, linking individual radiotherapy dose and fractionation information to subsequent outcome. The main focus will be on curative treatments for cancers of the bladder, brain, breast, head and neck, lung, prostate, rectum, upper urinary tract, lymphomas, skin, and gynaecological cancers (cervix and endometrium).

5.1 Primary Objective

The primary objective is to ascertain which radiotherapy fractionation schedules, including the total dose and the number of fractions in which the dose is delivered, are better than others at curing cancer in terms of reducing the rate of recurrence of the cancer and of cancer-related death. For cancers with long survivorship, such analyses will require follow-up of many years(15).

5.2 Secondary Objectives

The secondary objectives to be addressed are:

- to ascertain which radiotherapy fractionation schedules are better in terms of the risk of side-effects, both short-term and long-term.
- to ascertain whether the efficacy of radiotherapy depends on the levels of various blood measurements before treatment begins.

6. PURPOSE OF THE DATABASE

6.1 Summary of Design

This retrospective analysis will bring together data collected via the National Cancer Registration Service, linked together with chemotherapy, biochemistry, radiology, and pathology data collected at hospitals. The KIT (South East) will collate registry data and fully anonymise it, prior to sending it to the Clinical Trial Service Unit at the University of Oxford for analysis. Individual hospitals will link in chemotherapy, biochemistry, radiology, and pathology data, will remove the necessary identifiers, and send these anonymised additional data to the Clinical Trial Service Unit for final linkage and analysis. All data will be transferred via secure nhs.net mail data transfer provisions.

6.2 Data Description

6.2.1 Overall Description of data

Registry data

The initial study will make use of the datasets held at the Knowledge and Intelligence Teams, South East and East Midlands. Between 1999 and 2010, the then Oxford Cancer Intelligence Unit undertook a regional effort to collect detailed radiotherapy and chemotherapy data for the catchment area of the Thames Valley. Radiotherapy centres located within the Thames Valley (Oxford and Reading) and Northampton General Hospital submitted data on all patients treated with radiotherapy and/or chemotherapy during this period. Data for all radiotherapy and chemotherapy patients attending Leicester, Mount Vernon, and Hammersmith cancer centres, but resident in the Thames Valley area, were also obtained. Similarly, the then Trent Cancer Registry collected data on radiotherapy fractionation from Leicester (years 2004-2009), Lincoln (2007-2013), Nottingham (2008-2009), and Derby (2009-2011).

In total, the number of patients for whom data was obtained indicating that they received some form of radiotherapy was 31,821 during the years 2002 to 2010 at the former Oxford Cancer Intelligence Unit (data for 1999 to 2001 were not in usable form), and 11,573 during the years 2004 to 2011 at the former Trent Cancer Registry. If we include only data from those patients treated with curative intent, the number of patients for whom data is available for study at the two registries combined is 25,434.

Data held in the registries' radiotherapy datasets will be supplemented with information from the National Cancer Data Repository, National Radiotherapy Dataset (which began in April 2009), Cancer Waiting Times (for which national data are held at the Knowledge and Intelligence Team, East Midlands), and the Office of National Statistics (for up-to-date mortality data and urban/rural residence).

A note on geographical information and confidentiality

Geographical information will be important for this study, as it is likely that treatment received by individuals living further from treatment centres will differ from that of patients living nearer by. After discussions with the KIT South East, we believe that truncating post code at the fourth digit would make it more difficult to identify individuals than having the full post code, but would still provide sufficiently detailed information to make distances calculated from treatment centres meaningful. The study investigators and analysts will not make any attempts to identify individuals.

Outcome Data

Outcome information will be obtained from the Office of National Statistics and Hospital Episode Statistics, data which are held within the cancer registration system. This will be supplemented by hospital chemotherapy, pathology, radiology, biochemistry and haematology data for patients who have received radiotherapy. Pathology data will provide information on cancer recurrence or development of new primary cancer, radiology will provide information on cancer recurrence. Prostate specific antigen (PSA) levels before and after radiotherapy will be used to indicate risk grouping of prostate cancer prior to treatment

and to identify prostate cancer recurrence. Certain biochemical tests for example kidney and liver function will provide information on the severity of various side-effects.

In order to clarify whether the efficacy of radiotherapy is related to various blood test results before radiotherapy begins, haemoglobin levels and blood clotting data will also be collected. There is some evidence that low haemoglobin levels prior to radiotherapy may cause tumour resistance to radiotherapy (16-24). However this has not been studied for many cancer sites or for many clinical scenarios. Similarly, preclinical studies have shown that markers of blood clotting may also affect cancer outcomes. This study will examine whether blood clotting tests that are routinely measured in cancer patients are able to predict cancer outcomes or to predict response to radiotherapy in the clinic.

6.2.2 Inclusion Criteria

This study will include data from persons who have been registered with cancer and who have been treated with radiotherapy. In the first instance, the study will be limited to those living in the area covered by the former Oxford Cancer Intelligence Unit and diagnosed during 2002-2010 or in the former Trent Cancer Registry and diagnosed during 2004-2011. It is planned that the study will then be expanded to include patients registered in other areas and in other years.

6.2.3 Exclusion Criteria

Data from persons registered with cancer who have not been treated with radiotherapy will be excluded, as will all data from persons diagnosed with cancer in childhood (that is when aged less than 15 years), diagnosed with melanoma skin cancer only, and diagnosed with haematological cancers other than lymphoma.

6.3 Procedures

Data Transfer and Management

The process of data management and transfer is summarised below and in the study diagram in the Appendix.

1. Radiotherapy data held by the KIT (East Midlands) on patients treated in their area between 2004 and 2011 will be transferred to the KIT (South East).
2. The KIT (South East) will compile a single dataset for all the patients in the study. This will include the radiotherapy datasets (2002-2011) and items from the National Cancer Data Repository (demographics, diagnosis, Hospital Episode Statistics, mortality outcome).
3. The KIT (South East) will also prepare a list of unique anonymised identifiers for all patients in the study and add these anonymised identifiers to the dataset.
4. The KIT (South East) will also render postcodes and dates non-identifiable (by truncating postcodes at the fourth digit and abbreviating dates to include only month and year) and will remove identifiable postcode and date information.
5. The Cancer Waiting Times database (which records whether an individual who has been diagnosed with cancer has had a local or distant recurrence) is held for the whole of England by the KIT (East Midlands). The KIT (South East) will therefore send the dataset for all patients in the study (including the unique anonymous identifiers and any identifiers needed for linkage with Cancer Waiting Times) to the KIT (East Midlands).

6. The KIT (East Midlands) will link relevant items from Cancer Waiting Times to the dataset sent by the KIT (South East).
7. The KIT (East Midlands) will then remove all remaining identifiable information.
8. The KIT (East Midlands) will send this fully anonymised dataset containing all relevant information from the registries to the research team at Oxford University.
9. The research team at Oxford University will contact appropriate individuals in hospitals within the areas covered by the two KITs and seek agreement for hospital chemotherapy, pathology, radiology, biochemistry and haematology data to be made available to the study. Wherever this agreement is obtained, the Oxford University team will identify an 'appropriate person' within the hospital system to prepare the data.
10. The KIT (South East) will send a list of all relevant identifiers to each appropriate person (including NHS numbers, hospital numbers, names, and dates of birth). The list of identifiers will also include the unique anonymous identifiers generated for this study.
11. The appropriate persons will link their hospital data to the anonymised identifiers.
12. The appropriate persons will then strip all identifiable information from their datasets.
13. The appropriate persons will then send the anonymised hospital information to the research team at Oxford University.
14. The research team at Oxford University will link the hospital information with the dataset that they have received from KIT (East Midlands) via the anonymised identifiers created for this study.
15. The Oxford University research team will also carefully examine data for patients with multiple records and remove duplicates.
16. Finally, the team will conduct analyses and prepare reports for publication, with appropriate input from all collaborators, including members of the KIT teams.

Note that the research team at Oxford University have yet to establish formal contacts at the hospitals where it is hoped data will be obtained. Informal contacts have been initiated only at Oxford University Hospitals.

All transfer of data will occur via secure @nhs.net email addresses. Within the Clinical Trial Service Unit at Oxford University, the anonymised data will be stored in password−protected computer files on a server held behind a state−of−the−art proxying firewall. General access to the data will not be permitted, and access will only be given to those who will conduct analysis.

6.3.1 Informed Consent

This study is a retrospective analysis of data obtained by the KIT (South East) on behalf of researchers at the University of Oxford. Therefore individual patient consent is not required.

6.3.2 Data collection and Input

The data to be used in this study have already been or continue to be collected within routine data collection mechanisms. See the section "6.3 Procedures" above for a detailed description of data collection and input.

6.4 Policy/Management of RDB

All analyses will be conducted by the chief investigator and her immediate research team within the Clinical Trial Service Unit. The data will not be released to anyone else. Clinically significant results will be published in peer-reviewed journals and presented at conferences.

7. STATISTICS AND ANALYSIS

7.1 Size of dataset

The total number of patients for whom data is eligible to be included in the analysis is approximately 25,000. This is the total number of patients who have been identified as having received radiotherapy with curative intent in the records collected by the KIT (South East) between 2002 and 2010 and by the KIT (East Midlands) between 2004 and 2011, excluding haematological cancers, patients under the age of 15 years at time of diagnosis, and patients not resident in the Thames Valley or Trent at the time of diagnosis.

Data without sufficient information on number of fractions or without sufficient patient identification for the initial linkage at the KIT (South East) will not be included in the study. A power calculation was conducted using log rank survival methods, under the assumption that total numbers of fractions would be divided into high and low for each cancer site and all cancers analysed in a single analysis. Such a calculation revealed that a sample size of 20,000 (taking into account possible reduction in sample size due to missing values) and hazard ratio of 0.92 would result in a power of 84% (a hazard ratio of 0.85 in 99.9% and one of 0.95 in 45%).

7.2 Analysis

Standard survival analysis methods will be used to compare disease-free survival and other outcomes in patients with different dose/fractionation combinations and with different levels of quantities that have been measured in their blood before commencement of radiotherapy. Separate analyses will be carried out for each type of cancer. A combined endpoint may also be examined. The null hypothesis for each question to be answered in this study is that there is no effect of variation in number of fractions and total dose on outcomes. The alternative hypothesis is that there is some effect, the magnitude of which is not known at present. The effects of potential confounders and mediators will be examined, including type of cancer, calendar period, age, sex, stage, other treatments received, socio-economic status, trial-involvement and comorbidity.

8. ETHICS

The results of this study will help to improve the efficacy of treatment for future cancer patients. It will also help to reduce the risk of serious side-effects from cancer treatments. The study has, therefore, the potential to benefit large numbers of cancer patients in the future. The study also has the potential to benefit those patients who, in the future, need further cancer treatment. However, this is likely to be a minority of patients. The remainder will receive no direct benefit, but neither will they incur any burden. Patients whose data are included in this study will not be contacted. Ethical approval will be obtained through the National Health Service's Research Ethics Committee and Research and Development offices.

8.1 Participant Confidentiality

The only risk that might arise from the study is a breach of confidentiality of medical information. The use of patient-identifiable information is being kept to a minimum (see "6.3 Procedures" above) and only anonymised information will be passed to the researchers at Oxford University. Within the Clinical Trial Service Unit at Oxford University, the anonymised data will be stored in password−protected computer files on a server held behind a state−of−the−art proxying firewall. General access to the data will not be permitted, and access will only be given to those who will conduct analysis.

With regard to identifiability of treating clinician, no information on clinicians either at the hospital or at the GP level will be provided to CTSU. In the event that a treating clinician could be identified within any given treatment centre, no attempt will be made to do so and in the event that it happens inadvertently, the identity will not be communicated to anyone in any way.

With regard to being able to derive treatment start and end dates in some cases, no attempt will be made by the CTSU to identify these by calculations involving the maximum period in days between one month and another.

8.2 Other Ethical Considerations

There are no other ethical considerations.

9. DATA HANDLING AND RECORD KEEPING

See "6.3 Procedures" above for a description of data transfer procedures.

The university requires that all essential documents be retained for at least 5 years after the completion of a study. However, this is a valuable research resource and given that it is fully anonymous, we would like to retain it for as long as it may be useful in research. This is particularly true for cancers where survival is long, and for which long-term effects may only be seen many years after treatment (for example, heart disease after radiation to a field including the heart). We plan to store the data for 20 years after study completion.

The data will be stored in password−protected computer files on the secure server of the Clinical Trial Service Unit at the University of Oxford which is held behind a state−of−the−art proxying firewall. The analyses will be carried out by Johanna Rankin. Only she and her supervisors, Professor Sarah Darby and Dr. Carolyn Taylor, statistician advisor Dr. Paul McGale, and any other people directly involved in the study will have access the data.

10. FINANCING AND INSURANCE

The study will be funded in the first instance by the Oxford Cancer Research Centre Prize DPhil Studentship awarded to DPhil Candidate Johanna Rankin to cover her stipend and additional research costs. Any extra funding needs will be covered by the Clinical Trial Service Unit. The Clinical Trial Research Governance of the University of Oxford will serve

as sponsor of this study. The University of Oxford maintains Public Liability and Professional Liability insurance which will operate in this respect.

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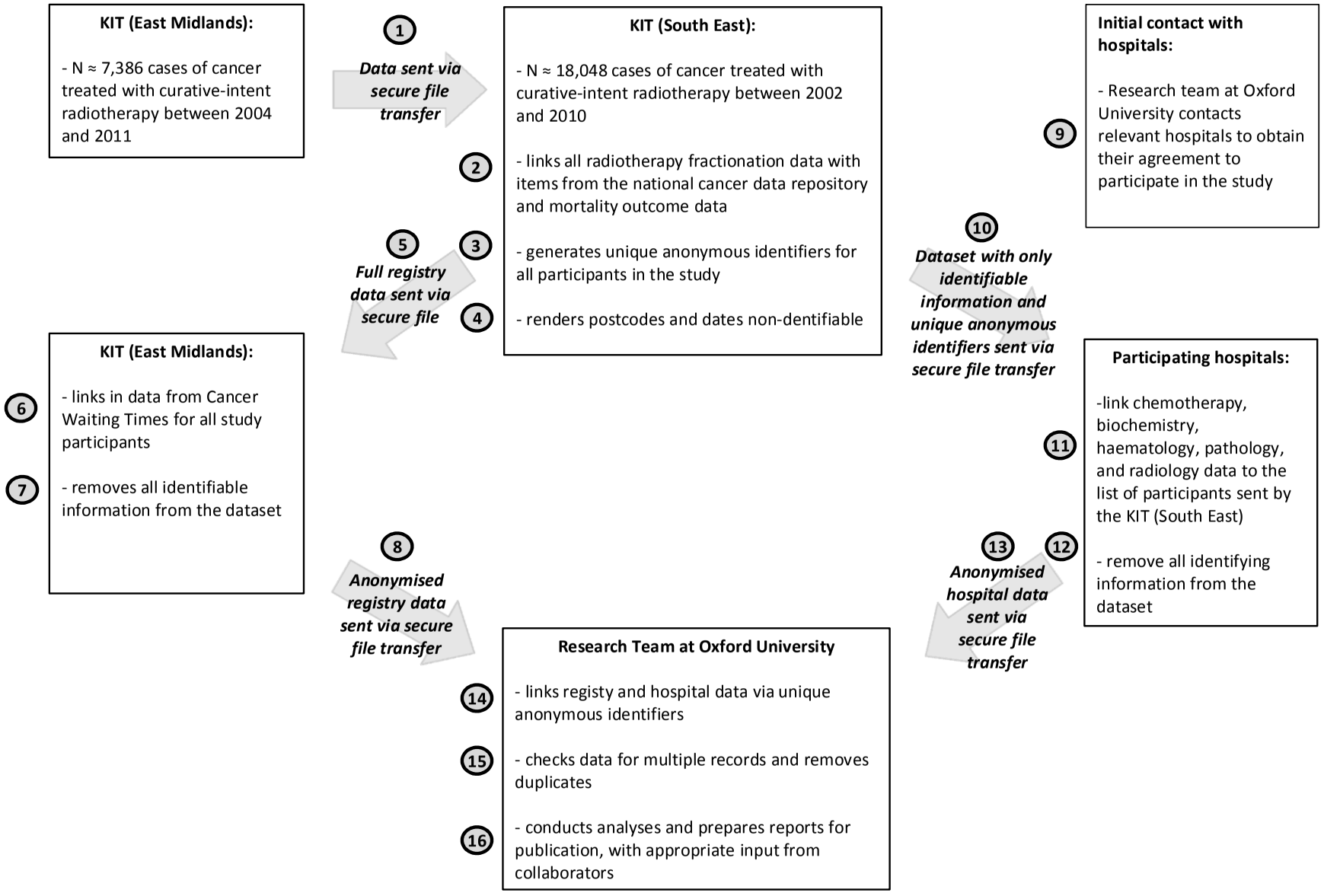
Figure 1: Diagram of the *Retrospective Analysis of the Effects of Different Radiotherapy Fractionation Schedules and of Differences in Blood Test Results on Outcomes in Cancer Patients*
Reference: 13/SC/0610



Appendix 3

Additional Material for Chapter 4

Figure 1

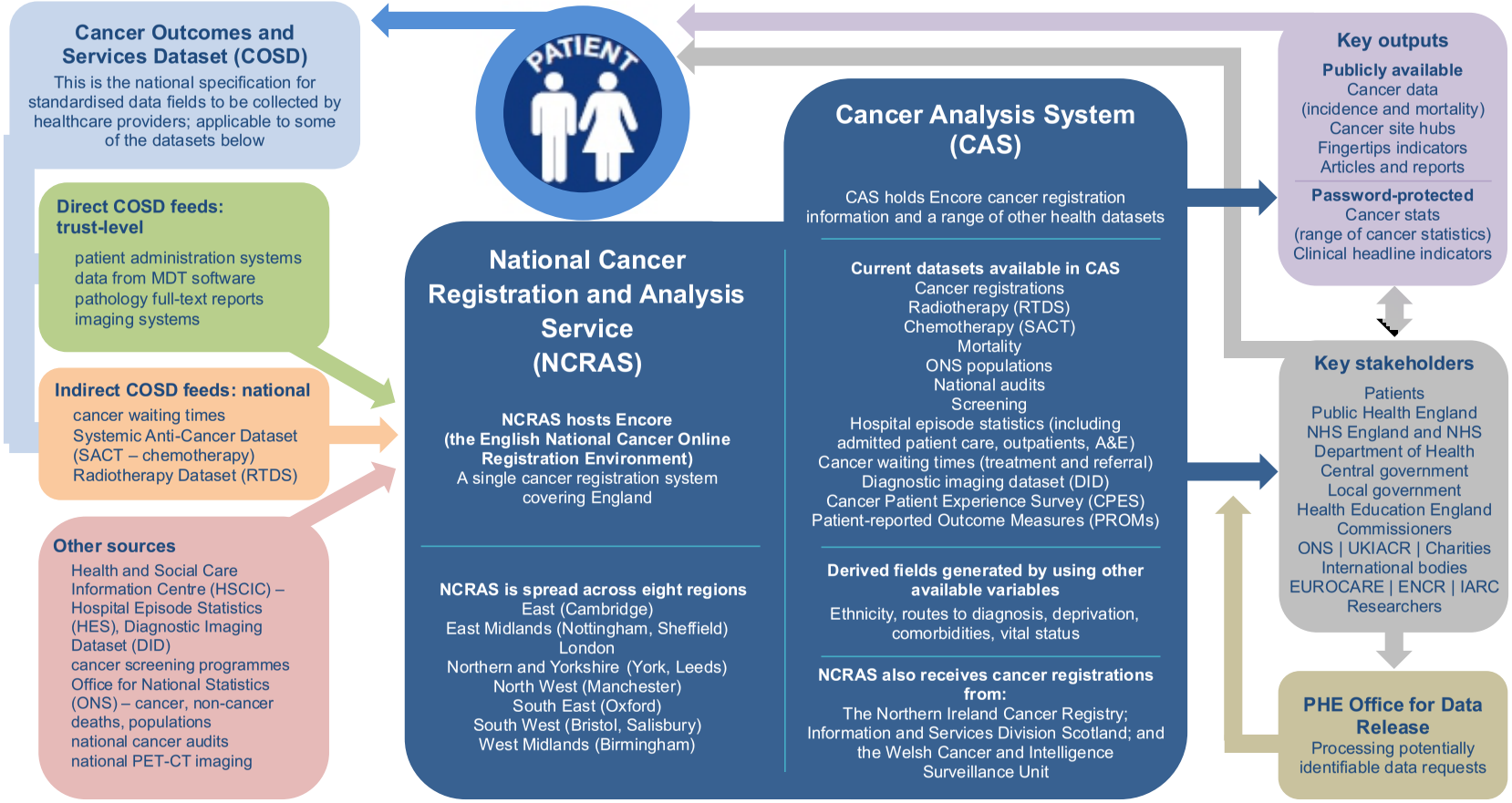
Public Health England

Protecting and improving the nation's health

Cancer data flows in Public Health England (PHE)

From the PHE National Cancer Registration and Analysis Service

This data flow diagram illustrates how the National Cancer Registration and Analysis Service (NCRAS) collects cancer data and transforms it into impactful intelligence. NCRAS delivers a world-class cancer registration service for England and generates analyses to drive improvements in prevention, standards of care and clinical outcomes for patients.



PHE publications gateway number: 2017085
Author: Sarah Miller Published: June 2017

Supplementary Text 1: Variables used in the PHE cohort study

Cancer site

Source dataset: CAS and CIA

If CAS and CIA data did not coincide in the cancer site indicated for a patient, in most cases these patients were dropped from analyses, as this was a possible indication that records in the two datasets did not match. However, in instances of very similar diagnoses (eg rectum and rectosigmoid junction, and some types of head and neck cancers), it was presumed that the two sites could be referring to the same tumour. It was presumed in these cases that the CAS diagnosis was more thoroughly verified and therefore this diagnosis was chosen as the correct one.

Age at diagnosis

Source dataset: CAS (date of diagnosis-date of birth)

Breast: age was grouped as 20-39, 40-49, 50-59, 60-69, 70-79, and 80+.

NSCLC: age was grouped as 38-58, 59-64, 65-70, 71-77, and 78-92. Age was grouped in this way in order to have even numbers of patients in each category.

DCIS: age was grouped as 20-49, 50-59, 60-69, and 70+.

Sex

Source dataset: CAS

Social deprivation (IMD)

Source dataset: UK government statistics published by the Department for Communities and Local Government, CAS (lower super output area code)

The English Indices of Multiple Deprivation (IMD) is an effort to gather information at the lower super output area (a UK census zoning area) level on the following seven domains: income deprivation; employment deprivation; education, skills and training deprivation; health deprivation and disability; crime; barriers to housing and services; and living environment deprivation (https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015). This information is then compiled in an index as a score and lower super output areas are ranked by this score. Lower super output areas are often grouped into quintiles by their score, as a proxy for socioeconomic status analyses. IMDs from the years 2004, 2007, 2010, and 2015 were used to obtain information on socio-economic status relevant to the women in this study. Quintiles were obtained using all lower super output areas in England.

After creating the quintiles, each patient's record was matched to their quintile, using lower super output area. A patient's lower super output area in CAS was recorded close to the time of diagnosis, and so their record was matched to the relevant wave of IMD, as done by PHE (see Appendix 2, Figure S3). Using the same principle, the 2016 IMD scores are based on 2011 data, so any women diagnosed in 2010 or 2011 were merged onto the 2016 IMD quintiles.

Number of positive nodes involved

Source dataset: CAS

Breast cancer only: This variable was coded into 0, 1 to 2, 3 or more, or unknown.

Stage

Source dataset: CAS, NSCLC notes project

NSCLC: See new variables from patients notes below.

Breast: Stage was grouped into 0-1B, 2-2B, 3-3B, 4, and unknown.

Chemotherapy, HER-2 treatment, and hormone therapy

Source dataset: CAS treatment data

NSCLC: Chemotherapy was coded as "yes" or "no". If a patient had any instance of curative-intent chemotherapy up to 93 days prior to the radiotherapy end date or up to 93 days after radiotherapy end date, they were coded as "yes". Otherwise they were coded "no", even if all treatment information was missing and therefore there was uncertainty as to whether there may be missing data. This variable was coded as yes/no because none of the 126 Oxford patients whose medical notes were reviewed showed any instance of having received chemotherapy that was not indicated in CAS (one patient had an instance of curative chemotherapy noted in CAS who had in fact not received any).

Invasive breast and DCIS: Just over half of any instance of chemotherapy in the CAS dataset had an accompanying non-missing field in a descriptive text variable. This text variable was used to code chemotherapy as cytotoxic, Her-2, missing, or other, if such treatment was received up to a year after date of diagnosis. This variable was cross-tabulated with recurrence outcomes in order to discern any patterns in the missing chemotherapy text variable as to whether patients might have received cytotoxic chemotherapy or not. It was determined that most women with missing chemotherapy details were likely to have received at least one round of cytotoxic chemotherapy, based on their recurrence and breast-cancer death outcomes compared to women whose details were not missing. Therefore any women with invasive breast cancer or DCIS who had an instance of curative-intent chemotherapy in CAS within one year before or after diagnosis were coded as "yes".

For women who had a non-missing text field indicating Her-2 treatment, these were coded as "yes" for HER-2 treatment if they received this within a year of diagnosis, and due to substantial underreporting of this treatment, all other women were coded as "unknown".

Hormone therapy was a separate treatment category. This variable was also underreported, so there were also two categories: "Yes" versus "unknown" for whether hormone therapy was received within a year after date of diagnosis.

Surgery

Source dataset: CAS treatment data, and HES for invasive breast/DCIS patients

NSCLC: Surgery was coded as "yes" or "no". If a patient had any instance of curative-intent surgery (defined as such within CAS) up to 93 days prior to the radiotherapy end date or up to 93 days after radiotherapy end date, they were coded as "yes". Otherwise they were "no", even if all treatment information was missing. This is because after review of patient notes in Oxford, there were no patients of the total 126 patient notes reviewed that showed a patient had received curative surgery that was not noted in the CAS data (there were three patients who were mistakenly coded as having received curative surgery when in fact they had not).

Invasive breast cancer/DCIS: Using the description that follows, an initial attempt was made using OPCS4 codes for surgical procedures in CAS to create a surgery type variable for invasive breast cancer and DCIS patients. However, it became clear that this variable was missing for too many

patients. Thus this same coding procedure was followed, using all data from CAS and directly from HES.

Using OPCS4 codes and the grouping of OPCS4 codes below, patients were coded as having received breast conserving surgery (BCS) or mastectomy, if there was an instance of either within three months of diagnosis (before or after). If a woman had BCS first that was followed by mastectomy within three months, she was coded as having a mastectomy, as sometimes BCS may not have wide enough margins to remove the full tumour. Any mastectomy occurring more than three months after BCS was considered to have been for a recurrence rather than for the initial tumour.

The OPC4 codes for common breast surgery procedures:
BCS: (B281, B282, B283, B285, B286, B287, B288, B289, B34, B341, B342, B343, B344, B345, B348, B349, B35)
Mastectomy: (B27, B271, B272, B27, B274, B275, B276, B278, B279)

Source: Gurdeep Mannu

Treatment centre

Source dataset: CIA

The CIA data were collected from data feeds that came to PHE (formerly the Oxford Cancer Intelligence Unit) directly from six treatment centres: Oxford, Reading, Northampton, Mount Vernon, Leicester, and Hammersmith, for patients who resided in the Thames Valley cancer registration area. Data was tagged by which centre they had come from, and therefore the CIA data were considered the more reliable source on where patients had received radiotherapy treatment (not CAS). There were not enough patients treated at Hammersmith, and so this centre was excluded. There were also not enough NSCLC patients treated at Mount Vernon, and so NSCLC patients from Mount Vernon were excluded.

Treatment year

Source dataset: CIA

The year of treatment was converted from the finish date of radiotherapy treatment (none of the patients were missing this variable, while 6% had missing start dates). This variable was grouped into three calendar periods: 2004-2006, 2007-2009, and 2010-2011.

Morphology

Source dataset: CAS

Lung: morphology was used to determine whether patients were non-small cell lung, small cell lung, or undefined.

Invasive breast cancer/DCIS: Morphology was a text variable which was coded into six categories as follows: ductal, lobular, ductal and lobular, tubular, mucinous, and other (Kezia Gaitskell, histopathologist, personal communication).

Laterality

Source dataset: CAS

Patients either had left-sided, right-sided, bilateral or unknown tumour locations.

Number of radiotherapy fractions

Source dataset: CIA

The intended number of fractions was derived by assuming that for a given centre, the intended number of fractions for non-standard regimens was the next highest number of standard fractions given at that centre. We assumed that the raw number of fractions variable consisted of a mix of number of fractions actually given and number of fractions intended. This seems probable when looking at dates of treatment, which cover a wide range of number of treatment days for a given number of fractions (Figures 4.6, 4.10, and 4.14). In some cases, dates may be wrong, but in other cases, the number of fractions indicated may be what was intended while the patient may have stopped treatment early, or had a break during radiotherapy.

Treatment time

Source dataset: CIA (and CAS)

Note: The CIA data contained start and end dates of treatment. 6% of start dates were missing and some of these could be replaced with CAS radiotherapy treatment dates, if the CAS dates were plausible in combination with CIA radiotherapy end dates. No treatment end dates are available in CAS.

Crude treatment time was calculated as the finish date of radiotherapy minus the start date of radiotherapy plus 1 (to include both the start and finish days). These days were then tabulated by numbers of fractions for both NSCLC and breast cancers, and also by centre and year for breast cancer. Based on the numbers of fractions and assumed dose-fractionation schedules for each cancer, a minimum and average number of treatment days were calculated (details for invasive breast cancer in Appendix 3, Figure S4). These calculated minimum and average numbers of treatment days were compared to the raw treatment dates indicated in the data in order to corroborate the assumed dose-fractionation schedules. If patterns discerned in the data were slightly different to calculations, the assumed minimum and average number of treatment days were adjusted to be closer to the raw data (eg. for the 20 and 25 fraction schedules in Leicester, there was an assumed additional 3 days of overall treatment time). Derived treatment time used in EQD2T calculations was the average treatment time derived from this process.

EQD2T

EQD2T was calculated using the same formula as in Chapter 2. The alpha-beta ratio for NSCLC was assumed to be 10, while it was assumed to 4 for breast cancer (1). Two types of EQD2T were calculated: estimated “intended” EQD2T and “actual” EQD2T. For intended EQD2T, average treatment time and assumed intended numbers of fractions were derived as explained above. For actual EQD2T, raw data were used to obtain treatment time and number of fractions, and patients were excluded whose values for number of fractions and treatment time were considered to be non-standard. Patients were permitted to have had up to three additional treatment days beyond the minimum days required, including weekends, to be included in actual EQD2T analyses.

For both types of EQD2T, dose per fraction was derived from assumed dose-fractionation schedules at each centre in a given year, based on dose-fractionations described in the 2006 RCR Report (2), raw treatment time patterns, and communication with consultant breast oncologists at Oxford, Reading, Northampton, and Mount Vernon (Leicester’s breast schedules were simpler and based on schedules at the other centres). See Tables 4.3 and 4.4 for assumed regimens for NSCLC and invasive breast/DCIS.

Measures of EQD2T in continuous models were centred at the mean value of intended EQD2T. For NSCLC that value was 53.3622 Gy. For breast cancer, that value was 44.62782 Gy (based on EQD2T excluding boost dose).

For descriptive analyses, actual EQD2T was grouped as there was a wide spread of values. For NSCLC, actual EQD2T was grouped as 35-51.5 Gy, 51.8 Gy, 52-53.9 Gy, 54-54.9 Gy, and 55-56 Gy. For breast cancer, actual EQD2T was grouped as 41-42.9 Gy, 43-43.9 Gy, 44-44.9 Gy, 45-45.9 Gy, 46-49.9 Gy, 50-51.9 Gy, 52-53.9 Gy, 54-55.9 Gy, and 56-59 Gy.

Variables used to "st-set" data in Cox regression (date of entry, date of exit, and event)

Date of entry into the study:

Source datasets: CAS, CIA

Either date of diagnosis (CAS) or start date of radiotherapy (CIA), whichever came sooner.

Date of exit:

Source of information: CAS

NSCLC, invasive breast cancer, and DCIS death analyses: 31 December, 2016 or prior date of death, or date of embarkation (departure from the United Kingdom)

Breast recurrence analyses: 31 December, 2015, or prior date of recurrence or death, or embarkation

DCIS and invasive breast cancer analysis: 30 April, 2016, or prior date of death, or date of embarkation

For all analyses, patients are also censored at date of second primary cancer diagnosis date, if applicable. Second primary cancers were determined to be such if records appeared to be genuine records and (a) they occurred at a different site in the body and at least 30 days after the diagnosis of the first tumour or (b) they occurred at the same site in the body at least 365 days after the diagnosis of the first tumour (except for contralateral breast cancer, which fell into category (a)). Patients with different tumour sites within 30 days were removed, as they had multiple primaries too close together. Data on second cancers are reliable in this analysis up to end of April, 2016, due to the lag time in cancer registration verification. Events:

Source datasets: death information from ONS, invasive cancer information from CAS, recurrence information from algorithm developed by colleagues at Oxford University and PHE using data from CAS, HES, and CWT

Overall survival: any death by 31 December, 2016

NSCLC death: any lung-specific death as coded according to underlying cause of death (ONS). Underlying causes of death considered to be NSCLC deaths were C342, C343, C383, C80, and C97. Cancer death codes not considered to be lung-specific were C159, C169, C250, C259, C329, C679, C920, and D329.

Breast cancer death: any underlying cause of breast cancer death (ONS) or breast cancer death identified in the recurrence algorithm. Underlying causes of death considered to be breast cancer deaths were C509, C710, C719, C787, C80, C800, C809, C97, and D432. Additionally, if patients had had a prior breast cancer recurrence, the following underlying causes of death were also considered to be breast cancer deaths: C220, C229, and C349.

Combined breast cancer event (recurrence, second invasive breast cancer or breast cancer death): a combination of breast cancer death as described above and of the following types of recurrence/second cancer as identified in the recurrence algorithm:

- Distant metastases of liver/NSCLC/bone/brain after three months
- Distant metastases in other locations after three months
- Palliative care after three months
- Recurrence in ipsilateral regional lymph nodes
- Recurrence in regional lymph nodes with no laterality recorded
- Recurrence in ipsilateral breast
- Recurrence, unknown location
- Contralateral breast/lymph node cancer

First occurrence of non-NSCLC second primary cancer (NSCLC only): Using the procedure as described in "Date of exit" above for second cancer identification, the first occurrence of cancer for NSCLC patients was identified. Cancers considered to be possibly related to the first primary NSCLC (C34 and C71) were not considered an event. Codes of cancers considered to be an event were C00, C12, C15, C16, C25, C43, C61, C64, C67, C83, C92, and C96.

First occurrence of invasive breast cancer (DCIS only): Using the same procedure as described above for second cancer identification, the first occurrence of cancer for DCIS patients was identified. If this first cancer occurrence was invasive breast cancer, this was considered an event in DCIS analyses.

New variables for Oxford NSCLC patients obtained from medical notes

Cancer stage

While stage is available as a variable in CAS, this was only available for 15% of NSCLC patients, and examining Oxford patient notes revealed that half of the non-missing CAS stage information for Oxford patients was in fact incorrect. CAS information on stage was thus not used in analyses. For patients whose notes were reviewed, TNM staging was available for most but not all (some patients simply had "1", "2" etc indicated), and therefore this variable was grouped into 1, 2, 3, 4 and missing.

Comorbidity

Any comorbidity reported in patients' notes was noted; however these appeared not always to be systematically reported. It was decided only to use reports of major cardiovascular or cerebrovascular conditions in our analyses, with patients coded as either "yes" or "no" for major comorbidity prior to or at the time of diagnosis. Major events included ischaemic heart disease, coronary heart disease, valvular heart disease, peripheral heart disease, cardio-vascular disease, myocardial infarction, cerebrovascular disease, and stroke.

Smoking status

Smoking status was available for all but six patients. If there was evidence that a patient had smoked up until their diagnosis of NSCLC and had then reported stopping, these were coded as current smokers. Any other ex-smoking, whether recent or long ago, was coded as ex-smoking. The remaining five patients were never-smokers. In final analyses, this variable was coded as "current smoker" and "ex/never-smoker".

Chemotherapy timing, relative to radiotherapy

While records of curative-intent chemotherapy are available in CAS together with a start date, it is not always possible to infer whether the chemotherapy preceded radiotherapy or overlapped with it. Review of the patient notes permitted patients to be categorised as having received no chemotherapy, sequential chemo-radiotherapy, or concurrent chemo-radiotherapy.

References

1. Ray KJ, Sibson NR, Kiltie AE. Treatment of Breast and Prostate Cancer by Hypofractionated Radiotherapy: Potential Risks and Benefits. Clinical oncology (Royal College of Radiologists (Great Britain)). 2015;27(7):420-6. Epub 2015/03/11.
2. Gildersleve J, Maher E, AJ M, Williams M. Radiotherapy Dose-Fractionation. London: Royal College of Radiologists, June 2006.

Supplementary Text 2: Documentation provided by PHE on the use of IMD data

Note: for the purposes of this DPhil, IMD scores were based on the full index and not just on income.

National Deprivation Scores for England

Each English cancer patient within the UKCIS is assigned a deprivation quintile based on their postcode at diagnosis.

Deprivation is measured using the Income Domain of the Indices of Multiple Deprivation. This measure is chosen (instead of the full Index of Multiple Deprivation) to avoid any risk of using an indicator circular on health. This is the most commonly used measure for deprivation in cancer patients, and was approved at a UKACR exec meeting as the standard methodology. The income domain of the IMD is available at Lower Super Output Area (LSOA) level, so each postcode can be mapped to an LSOA and then given a score.

Deprivation is measured at a point in time closest to the diagnosis date of the patient. The IMD were calculated in England in 2010 (based on 2008 data), 2007 (based on 2005 data) and in 2004 (based on 2001 data). Table 1 shows which measure of deprivation is used for patients diagnosed in a given year.

Table 1

	England
2009 **2008** **2007**	Income Domain of ID 2010 (2008 data)
2006 **2005** **2004** **2003**	Income Domain of ID 2007 (2005 data)
2002 **2001** **2000** **1999**	Income Domain of ID 2004 (2001 data)

Deprivation scores are not calculated for cases diagnosed before 1999, as IMD was not calculated prior to 2004, and the methodological differences between IMD and previous deprivation measures may be misleading. While historic deprivation scores are available, it is not possible to

make comparisons over time using these, and so they are not provided in the UKCIS to avoid misleading comparisons.

Although the IMD methodology aims to minimise changes between successive publications of deprivation scores, it is not possible to measure deprivation in an entirely consistent way, and comparisons over time may be misleading due to changing measures. Patients in the 'most deprived' quintile in 1999 cannot be assumed to be experiencing comparable levels of deprivation with patients in the 'most deprived' quintile in 2009. See the Communities and Local Governments website for a more detailed discussion of this.
http://www.communities.gov.uk/communities/research/indicesdeprivation/

For each measure of deprivation (2010, 2007 and 2004), deprivation scores for each LSOA are ranked, and the LSOAs of England are divided into five quintiles by deprivation, where 1 is the least deprived and 5 is the most deprived. Quintiles are produced to have equal populations. As cancer rates vary by deprivation, this does not mean each quintile has an equal number of cancer patients. As these quintiles are national, and deprivation varies across England, sub-national analyses may not have cancer patients in all quintiles. For example, analysis of an affluent area may have no cancer patients in quintile 5, the most deprived, as no patients in this area are in the 20% most deprived populations of England.

Deprivation scores are not calculated consistently across the UK. Patients in the 'most deprived' quintile in England cannot be assumed to be experiencing comparable deprivation to the 'most deprived' quintile in the Celtic countries, and direct comparisons should not be made.

This methodology was agreed by a subgroup of the UKACR analysis group, discussed by teleconference and email in June 2006.

Supplementary Text 3: Assumptions on doses, fractionations, and treatment times for invasive BC and DCIS patients

Note: this document refers to invasive breast cancer patients, but the assumption is that each of these centres in given years would have delivered the same regimens to DCIS patients as to invasive breast patients. Boosts are considered to be fractions as treatment dates were given including boosts given, and it is not known when treatments to the whole breast ended and boost treatments began. Tabulations include patients subsequently excluded due to missing surgery type.

1. Overview of numbers of fractions by centre for breast patients

There is a wide spread of numbers of fractions received by patients between 2004 and 2011 in Oxford, Reading, Northampton, Mount Vernon, and Leicester:

	centren_cia					
fxns_cia	Oxford	Reading	Northampt	Mount Ver	Leicester	Total
11	1	7	2	0	0	10
12	0	316	1	0	0	317
13	1,346	14	0	0	0	1,360
14	2	3	1	0	0	6
15	414	101	750	628	95	1,988
16	799	8	1	2	0	810
17	4	14	2	1	0	21
18	13	432	18	627	0	1,090
19	1	6	18	2	0	27
20	209	4	1,530	89	237	2,069
21	0	1	7	0	0	8
22	0	2	2	0	0	4
23	0	2	110	0	0	112
24	0	10	13	0	1	24
25	522	48	261	47	579	1,457
26	1	3	5	0	1	10
27	0	2	5	0	0	7
28	6	4	40	12	0	62
29	3	15	2	0	1	21
30	171	482	46	11	1	711
31	0	8	2	0	0	10
32	0	4	0	0	0	4
33	3	4	1	0	0	8
35	0	0	2	0	0	2
36	0	2	0	0	0	2
37	0	1	0	0	0	1
Total	3,495	1,493	2,819	1,419	915	10,141

Details of radiotherapy fractionations was derived at each centre for each of the numbers of fractions above, based on the 2006 Royal College of Radiologists' document on Radiotherapy Dose-Fractionation (1) and information obtained from contacts treating breast cancer at Oxford,

Reading, Northampton, and Mount Vernon. Patients who received non-standard numbers of fractions were assumed to have been intended to receive the next-highest number of regimens that was standard at their centre. Below are details for dose-fractionations and treatment times derived for each number of fractions at each centre in the given years of this study.

Based on the assumed dose-fractionation and treatment intervals (eg daily or every other day), a minimum and an average number of treatment days was calculated, giving equal chance to each day of the week (Monday-Friday) for a regimen to be started for a given patient. These were then compared with the actual treatment days recorded for patients to check the plausibility of the assumed treatment regimen.

2. 12 fractions in Reading

Assumed dose-fractionation: 40 Gy in 12 fractions, with 3 fractions given per week (every other day). No treatment on weekends.

For this regimen, the minimum number of treatment days was calculated to be 26, the maximum 28, and the average treatment time as 26.2 days. Here is the distribution of treatment days for patients treated with 12 fractions in Reading, by year of treatment:

start_to_finish	CIA YEAR							
	2005	2006	2007	2008	2009	2010	2011	Total
21	0	0	0	0	0	3	0	3
22	0	0	1	0	0	1	0	2
23	0	0	0	1	0	0	0	1
24	0	0	1	0	3	2	1	7
25	0	1	1	1	6	0	5	14
26	1	13	20	7	17	9	5	72
27	7	12	34	15	26	1	9	104
28	0	2	2	0	2	2	1	9
29	0	3	3	3	4	1	0	14
31	0	0	0	0	1	0	0	1
32	0	0	0	0	1	0	0	1
38	0	0	0	0	1	0	0	1
41	0	0	0	1	0	0	0	1
50	0	0	0	1	0	0	0	1
60	0	0	0	1	0	0	0	1
62	0	0	0	1	0	0	0	1
67	0	0	0	1	0	0	0	1
72	0	0	0	1	0	0	0	1
84	0	0	0	1	0	0	0	1
90	0	0	0	1	0	0	0	1
91	0	0	0	1	0	0	0	1
102	0	0	0	1	0	0	0	1
106	0	0	0	1	0	0	0	1
107	0	0	0	1	0	0	0	1
110	0	0	0	1	0	0	0	1
123	0	0	0	1	0	0	0	1
131	0	0	0	1	0	0	0	1
134	0	0	0	1	0	0	0	1
137	0	0	0	1	0	0	0	1
140	0	0	0	1	0	0	0	1
165	0	0	0	1	0	0	0	1
Total	8	31	62	46	61	19	21	248

3. 13 fractions in Oxford only

Assumed dose-fractionation: 41.6 Gy in 13 fractions, five fractions given per fortnight. No treatment on weekends.

For this regimen, the minimum number of treatment days was calculated to be 31, the maximum 33, and the average treatment time as 32.2 days. Here is the distribution of treatment days for patients treated with 13 fractions in Oxford, by year of treatment:

start_to_finish	CIA YEAR						
	2004	2005	2006	2007	2008	2009	Total
12	0	0	0	0	1	0	1
14	0	0	0	1	0	0	1
17	0	0	0	0	0	1	1
25	1	0	0	0	0	0	1
26	0	0	0	0	1	0	1
28	0	0	0	1	0	0	1
29	1	0	0	0	0	0	1
30	2	11	4	7	5	0	29
31	40	46	43	42	50	1	222
32	57	81	45	66	59	3	311
33	62	82	90	93	65	10	402
34	24	19	25	16	11	1	96
35	14	12	4	1	9	2	42
36	4	8	7	3	8	4	34
37	1	1	2	1	3	3	11
38	1	1	0	0	2	2	6
39	1	0	0	0	2	8	11
40	1	1	1	0	1	2	6
41	0	0	1	0	0	0	1
42	2	0	0	0	0	0	2
43	1	0	0	0	1	2	4
44	1	0	0	0	0	2	3
45	0	0	0	0	0	1	1
46	0	0	0	0	0	4	4
47	0	0	0	0	0	4	4
50	1	0	0	0	0	4	5
51	0	0	0	0	0	4	4
52	0	0	0	0	0	4	4
53	0	0	0	0	0	2	2
54	0	0	0	0	0	3	3
55	0	0	0	0	0	2	2
57	0	0	0	0	0	2	2
58	0	0	0	0	0	3	3
59	0	0	0	0	0	3	3
60	0	0	0	0	0	9	9
61	0	0	0	0	0	1	1
63	0	0	0	0	0	1	1
64	0	0	0	0	0	3	3
65	0	1	0	0	0	4	5
66	0	0	0	0	0	4	4
67	0	0	0	0	0	7	7
68	0	1	0	0	0	5	6
73	0	0	0	0	0	1	1
74	0	0	0	0	0	3	3
75	0	0	0	0	0	2	2
79	0	0	0	0	0	6	6
81	0	0	0	0	0	2	2
85	0	0	0	0	0	1	1
91	0	0	0	0	0	1	1
93	0	0	0	0	0	1	1
95	0	0	0	0	0	2	2
97	0	0	0	0	0	1	1
98	0	0	0	0	0	1	1
Total	214	264	222	231	218	132	1,281

4. 15 fractions

Assumed dose-fractionation: 40 Gy in 15 fractions, given daily. No treatment on weekends.

For this regimen, the minimum number of treatment days was calculated to be 19, the maximum 21, and the average treatment time as 20.6 days. Here is the distribution of treatment days for patients treated with 15 fractions **in Oxford**, by year of treatment:

start_to_finish	CIA YEAR 2004	2009	2010	Total
14	0	0	1	1
18	0	0	2	2
19	0	0	59	59
21	1	2	154	157
22	0	3	69	72
23	0	0	21	21
24	0	0	9	9
26	0	2	2	4
27	0	1	2	3
29	0	1	0	1
30	0	1	0	1
31	0	1	0	1
34	0	1	0	1
35	0	1	0	1
36	0	2	1	3
37	0	2	0	2
38	0	1	0	1
39	0	3	0	3
40	0	2	0	2
42	0	2	0	2
43	0	3	0	3
44	0	4	0	4
45	0	6	0	6
46	0	4	0	4
47	0	2	0	2
48	0	7	0	7
49	0	6	0	6
50	0	7	0	7
51	0	6	0	6
52	0	2	0	2
53	0	2	0	2
54	0	2	0	2
55	0	5	0	5
56	0	1	0	1
57	0	3	0	3
58	0	3	0	3
64	0	1	0	1
67	0	2	0	2
68	0	1	0	1
Total	1	92	320	413

Here is the distribution of treatment days for patients treated with 15 fractions **in Reading**, by year of treatment:

start_to_finish	CIA YEAR 2007	2008	2009	2010	2011	Total
11	0	0	1	0	0	1
19	0	0	1	1	12	14
20	0	0	0	0	1	1
21	1	0	5	1	31	38
22	0	1	3	4	20	28
23	0	0	0	1	2	3
24	0	0	0	5	0	5
25	0	0	0	1	2	3
26	0	0	0	3	0	3
31	0	0	1	1	0	2
34	0	0	0	0	1	1
50	0	1	0	0	0	1
Total	1	2	11	17	69	100

Here is the distribution of treatment days for patients treated with 15 fractions **in Northampton**, by year of treatment:

start_to_finish	CIA YEAR 2004	2005	2006	2007	2008	2009	2010	2011	Total
1	0	0	0	0	0	1	0	0	1
3	0	0	0	0	0	0	1	0	1
11	0	1	0	0	0	0	0	0	1
15	0	0	0	0	1	0	0	0	1
17	0	0	0	0	0	0	0	1	1
18	0	0	0	0	0	1	0	0	1
19	0	2	2	0	18	57	74	62	215
20	0	0	0	0	0	0	0	1	1
21	7	3	3	6	19	87	112	110	347
22	7	3	0	0	9	27	28	25	99
23	3	1	0	0	5	11	15	17	52
24	0	2	0	0	3	2	3	2	12
25	0	0	0	0	0	1	0	0	1
26	0	0	0	0	0	2	1	3	6
27	0	0	0	0	1	1	0	0	2
28	0	0	0	0	0	0	1	2	3
29	0	0	0	0	1	0	2	1	4
30	0	0	0	0	0	1	1	0	2
Total	17	12	5	6	57	191	238	224	750

Here is the distribution of treatment days for patients treated with 15 fractions **in Mount Vernon**, by year of treatment:

start_to_finish	CIA YEAR								
	2004	2005	2006	2007	2008	2009	2010	2011	Total
18	0	1	0	0	0	1	0	0	2
19	15	13	8	14	14	32	29	53	178
20	0	0	0	0	0	0	1	0	1
21	18	22	6	18	9	50	43	61	227
22	6	10	20	15	13	29	19	16	128
23	1	5	3	6	2	7	5	9	38
24	1	0	1	1	4	2	0	4	13
25	0	0	0	0	0	0	0	4	4
26	0	0	0	1	0	0	0	0	1
27	0	0	0	0	0	1	0	3	4
28	0	0	0	1	0	0	1	1	3
29	0	1	0	0	0	0	0	0	1
33	0	2	0	0	0	0	0	0	2
35	0	3	3	0	0	0	0	0	6
36	1	1	0	0	0	0	0	0	2
37	0	1	1	0	0	0	0	0	2
39	0	0	1	0	0	0	0	0	1
Total	42	59	43	56	42	122	98	151	613

Here is the distribution of treatment days for patients treated with 15 fractions **in Leicester**, by year of treatment:

start_to_finish	CIA YEAR			
	2004	2005	2006	Total
17	0	1	0	1
19	0	0	13	13
21	2	2	16	20
22	1	6	31	38
23	2	5	10	17
24	1	1	2	4
26	0	1	0	1
35	0	0	1	1
Total	6	16	73	95

5. 16 fractions in Oxford only

Assumed dose-fractionation: 41.6 Gy in 13 fractions, five fractions given per fortnight. Plus a boost of 7.5 Gy in three fractions, given in 3 fractions per week (every other day). No treatment on weekends.

For this regimen, the minimum number of treatment days was calculated to be 38, the maximum 40, and the average treatment time as 39.2 days.

Here is the distribution of treatment days for patients treated with 16 fractions in Oxford, by year of treatment:

start_to_finish	CIA YEAR 2004	2005	2006	2007	2008	2009	Total
7	0	1	0	0	0	0	1
11	0	0	1	0	0	0	1
13	1	0	0	0	0	0	1
14	0	0	0	1	0	0	1
29	1	0	0	0	0	0	1
30	0	0	1	1	0	0	2
32	1	0	2	0	0	0	3
33	2	3	0	0	1	0	6
34	0	0	0	1	0	0	1
35	0	0	0	0	1	0	1
37	10	2	6	4	0	0	22
38	14	20	32	26	22	4	118
39	39	28	30	43	38	5	183
40	34	33	40	48	42	11	208
41	6	15	2	3	2	2	30
42	7	8	10	3	0	0	28
43	16	9	10	8	5	2	50
44	7	5	3	0	0	7	22
45	1	5	0	1	1	4	12
46	1	1	0	0	1	5	8
47	0	0	0	0	0	3	3
48	1	0	0	0	0	0	1
50	0	1	0	0	0	0	1
51	0	0	0	0	0	2	2
52	0	0	0	0	0	1	1
53	0	0	0	0	0	3	3
57	0	0	0	0	0	1	1
58	0	0	0	0	0	1	1
60	0	0	0	0	0	3	3
61	0	0	0	0	0	2	2
62	0	0	0	0	0	2	2
63	0	0	0	0	0	2	2
64	0	0	0	0	0	2	2
65	0	0	0	0	0	2	2
66	0	0	0	0	0	3	3
67	0	0	0	0	0	2	2
68	0	0	0	0	0	6	6
71	0	0	0	1	0	1	2
72	0	0	0	0	0	4	4
74	0	0	0	0	0	2	2
75	0	0	0	0	0	2	2
78	0	0	0	0	0	1	1
79	0	0	0	0	0	1	1
80	0	0	0	0	0	1	1
81	0	0	0	0	0	3	3
82	0	0	0	0	0	4	4
87	0	0	0	0	0	1	1
88	0	0	0	0	0	2	2
89	0	0	0	0	0	1	1
92	0	0	0	0	0	2	2
93	0	0	0	0	0	1	1
96	0	0	0	0	0	1	1
102	0	0	0	0	0	1	1
107	0	0	0	0	0	1	1
124	0	0	0	0	0	1	1
Total	141	131	137	140	113	105	767

6. 18 fractions

Assumed dose-fractionation: 40 Gy in 15 fractions, given daily. Plus a boost of three daily fractions. No treatment on weekends.

For this regimen, the minimum number of treatment days was calculated to be 24, the maximum 26, and the average treatment time as 24.8 days.

In Reading, the three-fraction boost was 9 Gy. Here is the distribution of treatment days for patients treated with 18 fractions **in Reading**, by year of treatment:

start_to_finish	CIA YEAR 2006	2008	2009	2010	Total
5	0	0	1	0	1
13	0	1	0	0	1
14	0	0	0	1	1
18	0	0	0	1	1
19	0	0	2	0	2
21	0	0	1	0	1
22	0	0	1	0	1
23	0	0	3	1	4
24	1	29	80	62	172
25	0	9	33	9	51
26	0	21	23	7	51
27	0	14	17	13	44
28	0	9	11	4	24
29	0	6	5	3	14
30	0	2	5	0	7
31	0	0	1	0	1
33	0	1	0	0	1
34	0	1	0	0	1
36	1	1	1	0	3
38	0	1	0	0	1
56	0	2	1	0	3
57	0	0	1	0	1
64	0	1	0	0	1
72	0	1	0	0	1
73	0	1	0	0	1
74	0	1	0	0	1
77	0	2	0	0	2
80	0	2	0	0	2
84	0	2	0	0	2
87	0	2	0	0	2
90	0	1	0	0	1
92	0	1	0	0	1
93	0	3	0	0	3
98	0	1	0	0	1
102	0	2	0	0	2
103	0	1	0	0	1
104	0	1	0	0	1
105	0	1	0	0	1
106	0	1	0	0	1
108	0	1	0	0	1
112	0	1	0	0	1
114	0	1	0	0	1
115	0	2	0	0	2
118	0	3	0	0	3
119	0	1	0	0	1
120	0	2	0	0	2
121	0	1	0	0	1
125	0	1	0	0	1
129	0	1	0	0	1
144	0	1	0	0	1
147	0	1	0	0	1
151	0	1	0	0	1
Total	2	138	186	101	427

In Northampton, the three-fraction boost was also 9 Gy. Here is the distribution of treatment days for patients treated with 18 fractions **in Northampton**, by year of treatment:

start_to_finish	CIA YEAR 2008	2009	2010	2011	Total
24	0	1	8	4	13
25	0	0	1	1	2
27	0	1	1	0	2
29	1	0	0	0	1
Total	1	2	10	5	18

In Mount Vernon, the three-fraction boost was 10.5 Gy. For 2004, some of 2005, 2010, and 2011, it was assumed that the boost followed the main treatment. However, in some of 2005 and 2006-2008, it was assumed that the boost was integrated. This is because the minimum treatment time if patients received treatment consecutively is 24 (maximum 26), but if the boost was integrated, the minimum number of treatment days is 19 (average 20.6, maximum 21).

Here is the distribution of treatment days for patients treated with 18 fractions **in Mount Vernon**, by year of treatment:

start_to_finish	CIA YEAR 2004	2005	2006	2007	2008	2010	2011	Total
18	0	0	0	0	1	0	0	1
19	0	30	18	34	25	0	0	107
20	0	0	0	1	0	0	0	1
21	0	23	36	37	52	0	0	148
22	1	6	27	28	26	0	0	88
23	0	2	8	6	5	0	0	21
24	20	36	6	5	2	21	1	91
25	5	15	0	0	0	15	0	35
26	1	4	0	0	0	6	0	11
27	1	12	0	0	0	5	0	18
28	1	2	0	0	0	0	0	3
29	1	1	0	0	0	0	0	2
30	0	1	0	0	0	0	0	1
31	0	0	0	0	0	1	0	1
36	0	0	0	0	0	0	1	1
37	0	1	0	0	0	0	0	1
38	0	1	0	0	0	0	0	1
52	0	1	0	0	0	0	0	1
114	0	0	1	0	0	0	0	1
Total	30	135	96	111	111	48	2	533

7. 20 fractions

Assumed dose-fractionation **in Oxford and Mount Vernon**: 40 Gy in 15 fractions, given daily. Plus a boost of 10 Gy in 5 daily fractions. No treatment on weekends.

Assumed dose-fractionation **in Northampton and in Leicester**: 45 Gy in 20 fractions, given daily. No treatment on weekends.

For this regimen, the minimum number of treatment days was calculated to be 26, the maximum 28, and the average treatment time as 27.6 days.

Here is the distribution of treatment days for patients treated with 20 fractions **in Oxford**, by year of treatment:

start_to_finish	CIA YEAR 2008	2009	2010	Total
13	0	0	1	1
24	0	0	1	1
25	0	0	1	1
26	1	1	31	33
27	0	0	2	2
28	0	0	67	67
29	0	2	37	39
30	0	3	15	18
31	0	1	5	6
32	0	0	2	2
34	1	0	0	1
35	0	1	0	1
37	0	1	1	2
38	0	1	0	1
41	0	0	1	1
43	0	1	0	1
44	0	2	0	2
45	0	1	0	1
47	0	1	0	1
48	0	1	0	1
49	0	2	0	2
51	0	3	0	3
53	0	2	0	2
54	0	3	0	3
55	0	2	0	2
56	0	2	0	2
57	0	2	0	2
58	0	4	0	4
59	0	2	0	2
61	0	1	0	1
63	0	1	0	1
64	0	3	0	3
Total	2	43	164	209

For Mount Vernon, it looks as if the boost was simultaneously integrated, as most patients received treatment in 19 to 23 fractions.

Here is the distribution of treatment days for patients treated with 20 fractions **in Mount Vernon**, by year of treatment:

start_to_finish	CIA YEAR 2004	2005	2006	2007	2008	2010	Total
11	0	1	0	0	0	0	1
19	0	6	4	3	6	0	19
21	0	5	6	6	5	0	22
22	0	0	3	3	4	0	10
23	0	1	1	2	7	0	11
24	0	0	2	0	0	0	2
26	1	0	1	0	0	0	2
27	0	0	0	0	0	1	1
28	3	1	0	0	0	0	4
30	0	2	0	0	0	0	2
Total	4	16	17	14	22	1	74

Here is the distribution of treatment days for patients treated with 20 fractions **in Northampton**, by year of treatment:

start_to_finish	CIA YEAR								
	2004	2005	2006	2007	2008	2009	2010	2011	Total
5	0	0	0	0	0	0	1	0	1
7	0	0	1	0	0	0	0	0	1
9	0	0	0	0	0	1	0	0	1
11	0	1	0	0	0	0	0	0	1
16	0	0	0	1	0	0	0	0	1
19	0	0	0	0	0	1	4	0	5
21	0	0	0	0	0	2	1	0	3
22	0	0	0	0	0	1	0	1	2
23	0	0	0	0	0	0	1	0	1
24	0	1	0	0	0	0	0	0	1
25	1	1	1	0	0	1	0	0	4
26	44	43	57	84	74	33	17	12	364
27	1	0	1	4	2	0	0	0	8
28	74	71	81	80	92	35	23	27	483
29	67	57	52	52	50	24	20	9	331
30	31	34	10	25	25	13	9	6	153
31	10	19	25	22	13	0	0	4	93
32	5	0	3	1	2	3	1	0	15
33	2	2	4	2	2	0	0	0	12
34	3	2	3	2	1	0	0	0	11
35	2	1	1	2	3	0	0	0	9
36	0	0	0	1	1	0	0	0	2
37	0	0	0	1	2	0	0	0	3
38	1	1	0	1	1	0	0	0	4
39	0	0	1	0	0	0	0	0	1
40	0	0	0	1	0	0	0	0	1
42	0	0	0	0	1	0	0	0	1
45	0	0	1	0	0	0	0	0	1
57	0	1	0	0	0	0	0	0	1
91	0	0	1	0	0	0	0	0	1
307	0	1	0	0	0	0	0	0	1
Total	241	235	242	279	269	114	77	59	1,516

In **Leicester**, it appears there must have been a break of about three days in the treatment. The "normal" range of treatment days was considered for Leicester to be 29-30, with an average of 29.5 days.

Here is the distribution of treatment days for patients treated with 20 fractions **in Leicester**, by year of treatment:

start_to_finish	CIA YEAR 2004	2005	2006	Total
21	0	0	2	2
22	0	0	5	5
23	0	0	1	1
24	0	0	1	1
26	1	1	3	5
28	5	1	10	16
29	26	32	49	107
30	14	23	27	64
31	4	5	2	11
32	0	0	1	1
33	5	4	1	10
34	0	1	0	1
35	0	2	2	4
36	0	0	1	1
38	1	0	0	1
40	0	1	0	1
41	0	0	1	1
42	0	0	1	1
46	0	0	1	1
61	0	1	0	1
97	0	0	1	1
182	1	0	0	1
Total	57	71	109	237

8. 23 fractions in Northampton

Assumed dose-fractionation: 45 Gy in 20, given daily. Plus a three fraction boost of 9 Gy given daily. No treatment on weekends.

For this regimen, the minimum number of treatment days was calculated to be 31, the maximum 33, and the average treatment time as 31.8 days.

Here is the distribution of treatment days for patients treated with 20 fractions **in Northampton**, by year of treatment:

start_to_finish	CIA YEAR 2004	2005	2006	2007	2008	2009	2010	2011	Total
21	0	0	0	0	0	0	1	0	1
26	0	0	0	1	0	0	1	0	2
28	0	0	0	6	1	0	0	0	7
29	0	0	1	4	0	1	0	0	6
30	0	1	0	2	1	1	2	1	8
31	6	4	5	4	6	7	9	4	45
32	0	2	3	0	1	0	3	1	10
33	1	0	2	1	1	0	0	0	5
34	3	0	0	2	1	0	2	1	9
35	1	3	0	1	0	1	0	0	6
36	0	2	1	0	1	0	1	0	5
37	3	0	1	0	0	0	0	0	4
40	1	0	0	0	0	0	0	0	1
42	0	0	0	0	1	0	0	0	1
Total	15	12	13	21	13	10	19	7	110

9. 25 fractions

Assumed dose-fractionation: 50 Gy in 25, given daily. No treatment on weekends.

For this regimen, the minimum number of treatment days was calculated to be 33, the maximum 35, and the average treatment time as 34.6 days.

Here is the distribution of treatment days for patients treated with 25 fractions **in Oxford**, by year of treatment:

start_to_finish	CIA YEAR							
	2004	2005	2006	2007	2008	2009	2010	Total
30	0	0	1	0	0	0	0	1
32	0	1	1	0	0	0	0	2
33	16	9	15	14	29	0	9	92
34	1	0	3	0	0	0	0	4
35	7	15	21	29	28	3	18	121
36	6	14	11	17	23	5	14	90
37	4	14	9	9	15	2	13	66
38	3	3	9	2	15	3	6	41
39	5	1	1	0	1	1	1	10
40	0	1	0	2	1	1	1	6
41	2	1	0	0	1	6	1	11
42	0	0	3	0	1	1	1	6
43	1	1	0	0	2	8	0	12
44	0	0	0	0	1	2	1	4
45	0	0	0	0	0	1	0	1
46	0	0	0	0	0	1	0	1
47	0	0	0	0	0	2	0	2
49	0	0	0	0	1	1	0	2
50	0	0	0	0	0	1	0	1
51	0	0	0	0	0	1	0	1
52	0	0	0	0	0	1	0	1
53	0	0	0	0	0	2	0	2
54	1	0	0	0	0	0	0	1
55	0	0	0	0	0	2	0	2
56	0	0	0	0	0	4	0	4
57	0	0	0	0	0	6	0	6
58	0	0	0	0	0	1	0	1
59	0	0	0	0	0	3	0	3
60	0	0	0	0	0	1	0	1
61	0	0	0	0	0	3	0	3
62	0	0	0	0	0	1	0	1
63	0	0	0	0	0	3	0	3
64	0	0	0	0	0	1	0	1
65	0	0	0	0	0	2	0	2
67	0	0	0	0	0	1	0	1
71	0	0	0	0	0	3	0	3
72	0	0	0	0	0	2	0	2
76	0	0	0	0	0	2	0	2
77	0	0	0	0	0	2	0	2
78	0	0	0	0	0	2	0	2
79	0	0	0	0	0	1	0	1
81	0	0	0	0	0	1	0	1
82	0	0	0	0	0	1	0	1
86	0	0	0	0	0	1	0	1
Total	46	60	74	73	118	85	65	521

Here is the distribution of treatment days for patients treated with 25 fractions **in Reading**, by year of treatment:

start_to_finish	CIA YEAR 2005	2006	2007	2008	2009	2010	Total
1	0	0	0	0	0	1	1
33	0	0	1	0	0	0	1
35	1	1	4	0	1	0	7
36	2	2	7	1	0	0	12
37	0	2	8	1	0	0	11
38	0	1	1	0	0	0	2
39	0	1	0	1	0	0	2
40	0	1	0	0	0	0	1
42	0	1	0	0	0	0	1
43	0	1	0	0	0	0	1
44	0	0	0	1	0	0	1
102	0	0	0	1	0	0	1
122	0	0	0	1	0	0	1
Total	3	10	21	6	1	1	42

Here is the distribution of treatment days for patients treated with 25 fractions **in Northampton**, by year of treatment:

start_to_finish	CIA YEAR 2004	2005	2006	2007	2008	2009	2010	2011	Total
26	0	0	0	1	0	0	0	0	1
28	0	0	0	2	1	1	1	0	5
29	0	0	0	2	1	0	0	0	3
30	0	0	0	1	0	0	0	0	1
31	0	0	1	1	0	0	0	0	2
33	15	11	5	1	8	1	1	1	43
34	0	1	0	0	0	0	0	0	1
35	15	15	16	1	10	5	0	0	62
36	19	15	7	6	10	0	1	0	58
37	8	10	1	5	1	3	0	0	28
38	6	5	3	2	1	0	0	0	17
39	1	1	0	0	1	0	0	0	3
40	0	1	4	1	1	0	0	0	7
41	3	2	1	1	0	0	0	0	7
42	2	0	1	0	0	0	0	0	3
43	1	0	5	1	0	0	0	0	7
46	0	1	0	0	0	0	0	0	1
51	0	0	0	1	0	0	0	0	1
54	0	1	0	0	0	0	0	0	1
Total	70	63	44	26	34	10	3	1	251

Here is the distribution of treatment days for patients treated with 25 fractions **in Mount Vernon**, by year of treatment:

start_to_finish	CIA YEAR 2007	2008	2009	2010	2011	Total
33	3	1	3	1	6	14
34	0	1	0	0	0	1
35	1	1	1	6	7	16
36	1	2	1	2	0	6
37	1	1	1	1	0	4
38	1	0	1	0	2	4
39	0	1	0	0	0	1
40	0	0	1	0	0	1
Total	7	7	8	10	15	47

In **Leicester**, it appears there must have been a break of about three days in the treatment (however little it makes sense to take a break in this regimen). The standard range of treatment days for Leicester was considered to be 36-38, with an average of 37.

Here is the distribution of treatment days for patients treated with 25 fractions **in Leicester**, by year of treatment:

start_to_finish	CIA YEAR 2004	2005	2006	Total
15	0	0	1	1
26	0	0	1	1
27	0	1	0	1
29	0	6	10	16
30	1	1	3	5
31	0	0	1	1
32	0	1	0	1
33	1	4	4	9
34	0	2	0	2
35	7	1	9	17
36	39	43	62	144
37	44	133	55	232
38	3	26	14	43
39	2	9	7	18
40	7	27	15	49
41	4	9	10	23
42	5	1	0	6
43	1	0	0	1
44	0	2	0	2
46	1	0	0	1
47	0	1	0	1
48	0	1	0	1
49	1	0	0	1
54	1	0	0	1
55	0	1	0	1
60	1	0	0	1
Total	118	269	192	579

10. 28 fractions in Northampton

Assumed dose-fractionation: 45 Gy in 20 daily fractions. Plus a 16 Gy boost in 8 daily fractions. No treatment on weekends.

For this regimen, the minimum number of treatment days was calculated to be 38, the maximum 40, and the average treatment time as 38.8 days.

Here is the distribution of treatment days for patients treated with 28 fractions **in Northampton**, by year of treatment:

start_to_finish	CIA YEAR 2004	2005	2006	2007	2008	2009	Total
33	0	0	2	1	0	0	3
35	0	0	0	1	0	0	1
36	0	0	1	2	0	0	3
37	0	0	2	1	0	0	3
38	1	5	7	2	1	0	16
39	0	0	1	0	0	0	1
41	0	2	2	1	0	0	5
42	0	0	0	1	1	1	3
43	0	1	1	0	0	0	2
44	0	0	1	0	0	0	1
45	1	0	0	0	0	0	1
46	1	0	0	0	0	0	1
Total	3	8	17	9	2	1	40

11. 28 fractions in Mount Vernon

Assumed dose-fractionation: 50 Gy in 25 daily fractions. Plus an integrated boost of 10.5 Gy in 3 fractions. No treatment on weekends.

For this regimen, the minimum number of treatment days was calculated to be 33, the maximum 35, and the average treatment time as 34.6 days.

Here is the distribution of treatment days for patients treated with 28 fractions **in Mount Vernon**, by year of treatment:

start_to_finish	CIA YEAR 2005	2006	2007	2008	2010	Total
33	1	0	0	1	0	2
35	1	1	2	0	0	4
36	0	2	0	0	0	2
37	0	0	0	2	0	2
39	0	1	0	0	0	1
40	0	0	0	0	1	1
Total	2	4	2	3	1	12

12. 30 fractions

Assumed dose-fractionation: 50 Gy in 25 daily fractions. Plus a boost of 10 Gy in 5 fractions. No treatment on weekends.

For this regimen, the minimum number of treatment days was calculated to be 40, the maximum 42, and the average treatment time as 41.6 days.

Here is the distribution of treatment days for patients treated with 30 fractions **in Oxford**, by year of treatment:

start_to_finish	CIA YEAR							
	2004	2005	2006	2007	2008	2009	2010	Total
35	0	0	0	0	1	0	0	1
36	0	0	0	0	0	1	0	1
38	1	0	0	0	0	0	0	1
40	6	2	8	7	5	0	0	28
42	4	1	8	14	5	0	0	32
43	1	10	7	5	10	1	1	35
44	3	5	2	4	8	0	0	22
45	0	1	3	6	4	1	0	15
46	1	0	2	1	0	0	0	4
47	0	1	2	1	0	1	1	6
48	1	1	3	1	0	0	0	6
50	0	0	0	0	0	1	0	1
51	0	0	1	0	0	2	0	3
56	0	0	0	0	0	1	0	1
58	0	0	0	0	0	3	0	3
60	0	0	0	0	0	1	0	1
66	0	0	0	0	0	1	0	1
68	0	0	0	0	0	2	0	2
69	0	0	0	0	0	2	0	2
70	0	0	0	0	0	1	0	1
77	0	0	0	0	0	1	0	1
Total	17	21	36	39	33	19	2	167

In **Reading**, patients treated with 30 fractions in the year 2005 may have been non-standard (these patients were excluded in analyses of intended and actual EQD2T, including boost information). In 2006, it appears there may have been an integrated boost. For a regimen with integrated boost, the minimum number of treatment days was calculated to be 33, the maximum 35, and the average treatment time as 34.6 days.

Here is the distribution of treatment days for patients treated with 30 fractions **in Reading**, by year of treatment:

start_to_finish	CIA YEAR 2005	2006	2007	2008	2010	Total
5	2	0	0	0	0	2
7	12	0	0	0	0	12
9	2	0	1	0	0	3
21	0	0	0	0	1	1
23	0	0	0	0	1	1
26	0	0	0	0	1	1
29	0	0	0	1	0	1
33	0	27	0	0	0	27
35	3	47	1	0	0	51
36	0	30	5	0	0	35
37	1	7	2	0	0	10
38	0	13	1	0	0	14
39	0	1	0	0	0	1
40	0	4	11	0	0	15
42	1	2	28	0	0	31
43	0	0	25	0	0	25
44	0	1	13	13	0	27
45	0	0	6	1	0	7
46	0	0	1	0	0	1
47	1	0	1	0	0	2
48	0	1	1	0	0	2
51	0	0	1	0	0	1
52	0	0	0	1	0	1
56	0	0	1	0	0	1
59	0	0	1	0	0	1
72	0	0	1	1	0	2
73	0	0	1	0	0	1
85	0	0	0	1	0	1
90	0	0	1	0	0	1
91	0	0	0	1	0	1
92	0	0	0	1	0	1
146	0	0	0	1	0	1
151	0	0	0	1	0	1
166	0	0	0	1	0	1
Total	22	133	102	23	3	283

Here is the distribution of treatment days for patients treated with 30 fractions **in Northampton**, by year of treatment:

start_to_finish	CIA YEAR 2004	2005	2006	2007	2009	Total
19	0	0	0	0	1	1
26	0	0	0	1	0	1
33	0	0	0	1	0	1
36	0	0	1	3	0	4
37	0	0	0	2	0	2
40	2	0	3	0	0	5
41	0	0	0	1	0	1
42	2	3	1	0	0	6
43	1	1	4	0	0	6
44	0	1	0	1	0	2
45	1	2	2	1	0	6
46	0	0	0	1	0	1
47	0	0	0	1	0	1
48	0	0	2	0	0	2
Total	6	7	13	12	1	39

In **Mount Vernon**, the boost was again assumed to be integrated. For this regimen, the minimum number of treatment days was calculated to be 33, the maximum 35, and the average treatment time as 34.6 days.

Here is the distribution of treatment days for patients treated with 30 fractions **in Mount Vernon**, by year of treatment:

start_to_finish	CIA YEAR 2005	2006	2007	Total
33	1	0	0	1
35	1	1	0	2
36	0	3	3	6
37	0	1	0	1
38	0	1	0	1
Total	2	6	3	11

Reference

1. Gildersleve J, Maher E, AJ M, Williams M. Radiotherapy Dose-Fractionation. London: Royal College of Radiologists, June 2006.

Table 1: Hazard of breast cancer event, categorical intended radiotherapy dose including boost, and effect modifiers (N=8,768)*

EQD2T (Gy, including boost), Total dose (Gy) in no. fractions §	Effect modifiers: Boost dose (Gy) in no. fractions	Surgery type and boost status	No. events/ patients	HR	SE	95% CI	p_{Wald} †	p_{LR} ‡ test comparing this to simpler model
Model 7: Categorical model for dose, including boost dose, by type of surgery								Comparing to Model 5, Table 4.21
43.5, 45 in 20 (L)			23/43	2.80	0.67	(1.75, 4.47)	<0.0001	<0.0001
43.6, 50 in 25 (L)			122/531	0.91	0.13	(0.68, 1.20)	0.5	
44.2, 45 in 20 (N)			295/1,051	1.44	0.14	(1.19, 1.73)	<0.0001	
44.4, 40 in 15		BCS, no boost	226/1,204	**1**				
44.6, 50 in 25			133/417	1.30	0.15	(1.03, 1.63)	0.03	
45.4, 41.6 in 13 (O)			193/885	1.03	0.11	(0.83, 1.26)	0.8	
46.8, 40 in 12 (R)			13/22	2.39	0.69	(1.36, 4.22)	0.002	
50.8, 41.6 in 13 (O)	7.5 in 3		212/742	1.16	0.12	(0.95, 1.43)	0.2	
51.76, 50 in 25 (O, R, N)	10 in 5		82/323	0.88	0.12	(0.67, 1.15)	0.4	
51.80, 40 in 15 (O)	10 in 5		54/197	1.19	0.18	(0.88, 1.61)	0.3	
53.1, 45 in 20 (N)	9 in 3		26/114	0.99	0.21	(0.66, 1.50)	0.97	
53.4, 40 in 15 (R,N)	9 in 3		126/407	1.39	0.16	(1.12, 1.74)	0.003	
54.0, 40 in 15 (MV)	10 in 5	BCS, boost	15/83	0.91	0.25	(0.54, 1.55)	0.7	
54.6, 50 in 25 (R, MV)	10 in 5		36/131	1.21	0.23	(0.84, 1.75)	0.3	
55.8, 45 in 20 (N)	16 in 8		12/44	0.92	0.28	(0.51, 1.66)	0.8	
56.1, 40 in 15 (MV)	10.5 in 3		59/241	1.04	0.16	(0.77, 1.40)	0.8	
57.6, 40 in 15 (MV)	10.5 in 3		99/348	1.28	0.16	(1.00, 1.63)	0.05	
57.7, 50 in 25 (MV)	10.5 in 3		5/12	1.82	0.83	(0.75, 4.44)	0.2	
43.5/43.6, 45 in 20/ 50 in 25 (L)			72/136	1.72	0.30	(1.22, 2.41)	0.002	
44.2, 45 in 20 (N)			240/425	1.99	0.21	(1.62, 2.45)	<0.0001	
44.4, 40 in 15		Mastectomy	260/546	1.84	0.18	(1.52, 2.22)	<0.0001	
44.6, 50 in 25			185/332	1.72	0.19	(1.38, 2.13)	<0.0001	
45.4, 41.6 in 13 (O)			158/362	1.39	0.16	(1.11, 1.75)	0.004	
46.8, 40 in 12 (R)			67/172	1.21	0.17	(0.91, 1.60)	0.2	

* All models adjusted for chemotherapy, surgery, grouped age, number of nodes involved, stage, morphology, HER 2 treatment, and continuous calendar period in years. Patients treated in Reading in 2005 are not included as number of treatment days for these patients was not well reported.

† Wald test of association with outcome, separately for each category of variable, on one degree of freedom.

‡ Likelihood ratio test comparing more complex model with simpler model.

§ L=Leicester, N=Northampton, O=Oxford, R=Reading, MV=Mount Vernon

Abbreviations: BC=breast cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number. BCS=breast conserving surgery.

Table 2: Hazard of breast cancer event, categorical intended radiotherapy dose including boost, and effect modifiers (N=8,768)*

Treatment Centre	EQD2T (Gy, including boost)	Total dose (Gy) in no. fractions	Boost dose (Gy) in no. fractions	Type of surgery	No. events/ patients	HR	SE	95% CI	p_{Wald} †	p_{LR} ‡ test comparing this to simpler model
Model 8: Categorical model for dose, including boost dose, by type of surgery and centre										Comparing to Model 5, Table 4.21
Oxford	**44.4**	**40 in 15**		BCS	41/298	**1**				<0.0001
	44.6	50 in 25			50/131	2.48	0.53	(1.63, 3.77)	<0.0001	
	45.4	41.6 in 13			193/885	1.46	0.26	(1.03, 2.07)	0.03	
	50.8	41.6 in 13	7.5 in 3		212/742	1.65	0.29	(1.17, 2.34)	0.005	
	51.8	50 in 25	10 in 5		45/162	1.28	0.28	(0.82, 1.98)	0.3	
	51.8	40 in 15	10 in 5		54/197	1.69	0.35	(1.12, 2.54)	0.01	
	44.4	40 in 15		Mastectomy	34/85	2.05	0.48	(1.29, 3.24)	0.002	
	44.6	50 in 25			151/263	2.55	0.47	(1.78, 3.66)	<0.0001	
	45.4	41.6 in 13			158/362	1.96	0.36	(1.37, 2.81)	<0.0001	
Reading	44.4	40 in 15		BCS	12/74	0.66	0.22	(0.34, 1.27)	0.2	
	44.6	50 in 25			9/44	1.49	0.55	(0.72, 3.09)	0.3	
	46.8	40 in 12			13/22	3.29	1.06	(1.75, 6.18)	<0.0001	
	51.8	50 in 25	10 in 5		21/118	1.05	0.29	(0.62, 1.80)	0.8	
	53.4	40 in 15	9 in 3		122/389	1.98	0.36	(1.39, 2.83)	<0.0001	
	54.6	50 in 25	10 in 5		33/120	1.71	0.41	(1.07, 2.74)	0.03	
	44.4	40 in 15		Mastectomy	8/13	2.24	0.88	(1.04, 4.84)	0.04	
	44.6	50 in 25			6/14	1.79	0.79	(0.75, 4.24)	0.2	
	46.8	40 in 12			67/172	1.68	0.34	(1.13, 2.51)	0.01	
Northampton	44.2	45 in 20		BCS	295/1,051	2.04	0.35	(1.46, 2.86)	<0.0001	
	44.4	40 in 15			99/477	1.77	0.33	(1.23, 2.56)	0.002	
	44.6	50 in 25			68/226	1.55	0.32	(1.04, 2.33)	0.03	
	51.8	50 in 25	10 in 5		16/43	1.52	0.46	(0.84, 2.76)	0.2	
	53.1	45 in 20	9 in 3		26/114	1.41	0.36	(0.86, 2.32)	0.2	
	53.4	40 in 15	9 in 3		4/18	1.36	0.71	(0.48, 3.80)	0.6	
	55.8	45 in 20	16 in 8		12/44	1.30	0.43	(0.67, 2.50)	0.4	
	44.2	45 in 20		Mastectomy	240/425	2.81	0.50	(1.99, 3.99)	<0.0001	
	44.4	40 in 15			109/227	2.86	0.53	(1.99, 4.12)	<0.0001	
	44.6	50 in 25			19/33	2.46	0.71	(1.40, 4.31)	0.002	
Mount Vernon	44.4	40 in 15		BCS	58/275	1.69	0.35	(1.13, 2.53)	0.01	
	44.6	50 in 25			6/16	2.72	1.20	(1.15, 6.45)	0.02	
	54.0	40 in 15	10 in 5		15/83	1.30	0.40	(0.71, 2.38)	0.4	
	54.6	50 in 25	10 in 5		3/11	1.82	1.10	(0.56, 5.92)	0.3	
	56.1	40 in 15	10.5 in 3		59/241	1.48	0.31	(0.97, 2.23)	0.07	
	57.6	40 in 15	10.5 in 3		99/348	1.81	0.35	(1.24, 2.63)	0.002	
	57.7	50 in 25	10.5 in 3		5/12	2.60	1.24	(1.02, 6.60)	0.05	
	44.4	40 in 15		Mastectomy	107/216	2.59	0.50	(1.78, 3.78)	<0.0001	
	44.6	50 in 25			9/22	1.45	0.54	(0.70, 3.00)	0.3	
Leicester	43.5	45 in 20		BCS	23/43	3.98	1.13	(2.27, 6.95)	<0.0001	
	43.6	50 in 25			122/531	1.29	0.27	(0.85, 1.95)	0.2	
	44.4	40 in 15			16/80	1.46	0.46	(0.79, 2.71)	0.2	
	43.5/43.6	45 in 20/50 in 25		Mastectomy	72/136	2.44	0.57	(1.54, 3.85)	<0.0001	
	44.4	40 in 15			2/5	2.26	1.66	(0.54, 9.50)	0.3	

* Model adjusted for chemotherapy, surgery, grouped age, number of nodes involved, stage, morphology, HER 2 treatment, and continuous calendar period in years. Patients treated in Reading in 2005 are not included as number of treatment days for these patients was not well reported.

† Wald test of association with outcome, separately for each category of variable, on one degree of freedom.

‡ Likelihood ratio test comparing more complex model with simpler model.

Abbreviations: BC=breast cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number. BCS=breast conserving surgery. HER-2=human epidermal growth factor receptor 2.

Table 3: Overall survival, continuous intended EQD2T (N=8,879)

	Effect modifier	No. events/ patients	HR	SE	95% CI	p_{Wald}*	Joint p_{LR}†	p_{Wald}‡ trend
Continuous intended EQD2T, excluding boost information								
Trend per Gy	BCS	1,001/6,906	1.03	0.06	(0.91, 1.24)	0.6	-	-
EQD2T	Mastectomy	600/1,973	0.94	0.05	(0.82, 1.06)	0.3	-	-
Age (years)								
20-40		105/501	1.32	0.15	(1.06, 1.65)	0.01	<0.0001	-
40-50		215/1,686	0.87	0.08	(0.73, 1.03)	0.1		
50-60		337/2,655	1					
60-70		438/2,650	1.58	0.12	(1.37, 1.83)	<0.0001		
70-80		375/1,159	2.98	0.24	(2.54, 3.48)	<0.0001		
80+		131/228	7.04	0.77	(5.68, 8.73)	<0.0001		
Number of nodes involved								
0		606/4,807	1				<0.0001	<0.0001§
1-3		382/1,932	1.19	0.09	(1.03, 1.37)	0.02		
4 or more		339/825	2.43	0.20	(2.06, 2.85)	<0.0001		
Unknown		274/1,315	1.18	0.11	(1.00, 1.41)	0.06		
Cancer stage								
0-1A		305/2,388	1				0.0002	<0.0001§
2-2B		615/2,424	1.30	0.11	(1.11, 1.53)	0.001		
3-3A		149/419	1.59	0.19	(1.27, 2.00)	<0.0001		
Unknown		532/3,648	1.38	0.12	(1.16, 1.64)	<0.0001		
Morphology								
Ductal		1,282/6,945	1				0.0001	-
Lobular		169/891	0.79	0.07	(0.67, 0.93)	0.005		
Ductal and Lobular		61/309	0.95	0.12	(0.73, 1.22)	0.7		
Tubular		21/295	0.51	0.11	(0.33, 0.79)	0.003		
Mucinous		18/152	0.55	0.13	(0.35, 0.88)	0.01		
Other/Unspecified		50/287	1.01	0.15	(0.76, 1.34)	0.96		
Trend across calendar period (2004-2011)								
Change per year		1,601/8,879	0.91	0.02	(0.88, 0.94)	<0.0001	-	-
Cytotoxic Chemotherapy								
No		1,016/5,891	1				-	-
Yes		585/2,988	1.20	0.08	(1.06, 1.37)	0.005		
Surgery type, effect calculated at mean EQD2T (44.63Gy)								
BCS		1,001/6,906	1				-	-
Mastectomy		600/1,973	1.52	0.10	(1.35, 1.72)	<0.0001		
HER-2 treatment								
Unknown		1,579/8,704	1				-	-
Any		22/175	0.82	0.18	(0.53, 1.26)	0.4		

* Wald test of association with outcome, separately for each category of variable, on one degree of freedom.

† Joint likelihood ratio test of association with outcome, of variable including all *n* categories, on (*n* -1) degrees of freedom.

‡ Wald test for linear trend across variable.

§ Test excludes patients missing information on this variable.

Abbreviations: HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number. IMD=indices of multiple deprivation. BCS=breast conserving surgery. HER-2=human epidermal growth factor receptor 2.

Table 4: Non breast cancer survival, adjusted for all available factors and indicating degree of confounding by each factor (N=8,879)

			No. events/ patients	HR	SE	95% CI	p_{Wald}*	Joint p_{LR}†	p_{Wald}‡ trend	Degree of confounding§
EQD2T (Gy)	**Total dose (Gy) in no. fractions**	**Centre**								
43.5	45 in 20	Leicester	11/177	0.59	0.22	(0.28, 1.22)	0.2	0.009	0.6	-
43.6	50 in 25	Leicester	39/533	0.51	0.12	(0.32, 0.80)	0.003			
44.2	45 in 20	Northampton	131/1,634	1.19	0.16	(0.91, 1.56)	0.2			
44.4	40 in 15	All	159/3,026	1						
44.6	50 in 25	All but Leicester	52/1,426	0.80	0.13	(0.57, 1.11)	0.2			
45.4	41.6 in 13	Oxford	172/1,989	1.00	0.13	(0.78, 1.28)	0.99			
46.8	40 in 12	Reading	14/194	0.97	0.29	(0.54, 1.74)	0.9			
Boost to tumour bed										None
No			419/6,126	1				-	-	
Yes			159/2,753	0.96	0.11	(0.77, 1.2)	0.7			
Age (years)										Major
20-40			4/501	0.24	0.13	(0.09, 0.67)	0.006	<0.0001	<0.0001	
40-50			16/1,686	0.29	0.08	(0.17, 0.49)	<0.0001			
50-60			95/2,655	1						
60-70			179/2,650	2.12	0.27	(1.65, 2.73)	<0.0001			
70-80			202/1,159	5.83	0.77	(4.50, 7.56)	<0.0001			
80+			82/228	16.35	2.66	(11.89, 22.48)	<0.0001			
Number of nodes involved										Major
0			299/4,807	1				0.3	0.5¦	
1-3			121/1,932	1.08	0.14	(0.84, 1.38)	0.6			
4 or more			50/825	1.17	0.21	(0.82, 1.67)	0.4			
Unknown			108/1,315	1.36	0.21	(1.00, 1.85)	0.05			
Cancer stage										None
0-1A			177/2,388	1				0.9	0.9¦	
2-2B			195/2,424	1.05	0.13	(0.82, 1.34)	0.7			
3-3A			32/419	1.11	0.25	(0.71, 1.73)	0.7			
Unknown			174/3,648	1.09	0.15	(0.84, 1.42)	0.5			
Morphology										
Ductal			444/6,945	1				0.2	-	None
Lobular			65/891	0.89	0.12	(0.68, 1.16)	0.4			
Ductal and Lobular			21/309	1.05	0.24	(0.67, 1.63)	0.8			
Tubular			16/295	0.77	0.20	(0.46, 1.27)	0.3			
Mucinous			10/152	0.53	0.17	(0.28, 0.99)	0.05			
Other/Unspecified			22/287	1.18	0.26	(0.76, 1.81)	0.5			
Social deprivation (quintiles of IMD score)										Moderate
Least deprived			239/4,220	1				<0.0001	<0.0001	
2nd			125/2,121	1.06	0.12	(0.85, 1.32)	0.6			
3rd			96/1,183	1.38	0.17	(1.09, 1.76)	0.008			
4th			73/921	1.44	0.19	(1.10, 1.87)	0.007			
Most deprived			45/434	2.18	0.36	(1.57, 3.02)	<0.0001			
Trend across calendar period (2004-2011)										Moderate
Change per year			578/8,879	0.92	0.03	(0.86, 0.98)	0.006	-	-	
Cytotoxic Chemotherapy										None
No			490/5,891	1				-	-	
Yes			88/2,988	0.84	0.11	(0.64, 1.09)	0.2			
Surgery type										None
BCS			442/6,906	1				-	-	
Mastectomy			136/1,973	1.12	0.15	(0.86, 1.46)	0.4			
Hormone therapy										None
Unknown			455/7,119	1				-	-	
Yes			123/1,760	0.90	0.10	(0.72, 1.11)	0.3			
HER-2 treatment										None
Unknown			455/7,119	1				-	-	
Yes			123/1,760	0.69	0.41	(0.22, 2.19)	0.5			

* Wald test of association with outcome, separately for each category of variable, on one degree of freedom.
† Joint likelihood ratio test of association with outcome, of variable including all *n* categories, on (*n* -1) degrees of freedom.
‡ Wald test for linear trend across variable.
§ Degree of confounding was assessed by examining this full model with a model excluding each of the potential confounders, one by one. See Methods for detailed explanation.
¦ Test excludes patients missing information on this variable.

Abbreviations: BC=breast cancer. HR=hazard ratio. SE=standard error. EQD2T= time-corrected equivalent dose in 2 Gy fractions. No.=number. IMD=Indices of Multiple Deprivation. BCS=breast conserving surgery. HER-2=human epidermal growth factor receptor 2.

Supplementary Text 4: Programmes created to manage all data for the PHE cohort study

Below is a list all programmes in Stata used to manage all data used in the cohort study. The list includes the name of the programme, date it was created, description of what it does, and the latest output files generated. Where relevant, it also indicates the number of patients remaining in the final datasets created.

1. TransferRawOxData

- Created: 19 March 2014
- A simple do-file for transferring Thames Valley CIA data from an Access database to Stata. The Access database was last updated by Ann Watters on 18 March 2014. N=73511.
- Most recent data output: CIA20140321_28Mar2014.dta (N=73,511)

2. DataManage

- Created: 26 March 2014
- Manages Thames Valley CIA data
- Cleans NHS numbers, names, birthdates
- formats date variables, creates numeric variables from string (including cancer site), age variable
- Creates intent variable based on Ken Lloyd & Sue Forsey's definitions and Carolyn's input
- Most recent data output: CIASE_5Sep2014.dta (N=**73,511**)

3. DataElig

- Created: 26 March 2014
- Creates CIA dataset with only eligible patients, based on the study protocol: age, cancer site, intent (number of fractions), type of radiotherapy
- Most recent data outputs: CIASEelig_5Sep2014.dta (all patients, but with eligibility variables, N=73,511), CIASEeligonly_5Sep2014.dta (only patients to be included, N=25,063)

4. OCIUnhsntrace

- 12 May 2014
- Initial attempt at capturing more patients, without NHS numbers (match to NCDR via (1) first name, surname and dob and (2) surname and date of birth
- Most recent data output: CIASEeligonlyupdate_11Sep2014.dta (N=25,063)

5. RebeccaTrace

- 26 June 2014
- Further attempt at cleaning up missing NHS numbers. Almost all remaining missing NHS numbers are resolved (originally 967 missing NHS number)
- Most recent data output: CIASEeligupdateRebecca_11Sep2014 (N=**25,063**)

5. DataDeduplicate

- 8 May 2014
- Deduplicate CIA dataset
- Started working on deduplication by the variable types that contained differing information. Then moved through deduplication by cancer site, working in blocs.
- Labelled 149 individuals as having a recurrence and 90 individuals as having a second cancer (85 of the latter are also tagged as having a second primary cancer in CAS). A "recurrence" was if tumour same site, a second cancer if different site – however, such "recurrence" information was not reliable and not subsequently used.
- Most recent data output: CIASEdedup_23Jan2015 (N=**24,119**) [Note: The final run of this before giving it to Rebecca Girdler to produce first CAS file was 16 September 2014, but I kept working on deduplication until 23 January 2015, so that she could go ahead and run the export from CAS. Hence this later date.]

6. RebCasMerge

- 16 September 2014
- Simple do-file that gets deduplicated CIA data to merge with CAS, forces last duplicates not resolved in #5 above and creates excel sheet of identifiers for Rebecca Girdler to merge with CAS.
- Data output: CIASEdedupRebCasMerge_16Sep2014.xls (note that this file with the same name is also in fromKITS folder with all the original data merged in by Rebecca Girdler) (N=24,074). The file was last updated 17 September 2014. Unfortunately only requested a subset of variables to work with at first, rather than all variables, so would have to go and find any additional information with Rebecca again, if needed for individuals excluded from the full CAS merge that happened later on.

7. AppendCASclean

- 10 October 2014
- Rebecca Girdler did three different exports. Most patients could be matched on NHS number, but some were missing NHS number and so were merged on first name, surname, and date of birth (not necessary for post code to be the same); for those without a match on these, a further merge was done on exact post code and date of birth (with manual checking of first and last name). This merge was not restricted in any other way and the earliest diagnosis date was 1957. Records were later restricted to only those with invasive cancer (except DCIS); malignant non-melanoma skin cancers were excluded

as cancers of interest. Any patients with prior cancers could thus be excluded from further analysis.

- In order to simplify the CAS extract and merge with CIA data, only variables regarded as key identifiers were obtained in this initial extract: cancer site, date of diagnosis, patient identifiers, first name, surname, post code, sex, and birth date.
- This do-file deduplicates data across the three exports produced by Rebecca Girdler, then appends them together and merges this together with CIA data.
- There are up to seven multiples per NHS number. These were ordered by diagnosis date, saving separate datasets for each subsequent record.
- Most recent outputs: AppendCAScleanWithMults_26Jan2015.dta (full dataset with multiples, N=28,744), AppendCASclean_26Jan2015 (first registrations, no multiples, N=**23,811**), then for the subsequent records:
- AppendCASclean2ndRegs_26Jan2015 (N=4,274)
- [Investigate AppendCASclean2ndRegs_26Jan2015_18Mar2015 (N=20,833)]
- AppendCASclean3rdRegs_26Jan2015 (N=540)
- AppendCASclean4thRegs_26Jan2015 (N=88)
- AppendCASclean5thRegs_26Jan2015 (N=21)
- AppendCASclean6thRegs_26Jan2015 (N=7)
- AppendCASclean7thRegs_26Jan2015 (N=3)

8. MergeCIA_CASprelim

- 14 October 2014
- This programme sorts through the merge of CIA and CAS data in blocs in terms of match of cancer site and dates of treatment/diagnosis and in terms of multiples or single registrations. An original merge of the first CAS record and CIA records is conducted, and each subsequent CAS record is merged in wide into this file.
- The data reports DataReport_20141106.doc, DataReport_20141216.doc, DataReport_20150203.doc, and DataReport_20150320.doc help to explain the process of this long programme.
- Here is a summary of the steps followed for the merge of the CAS and CIA data:

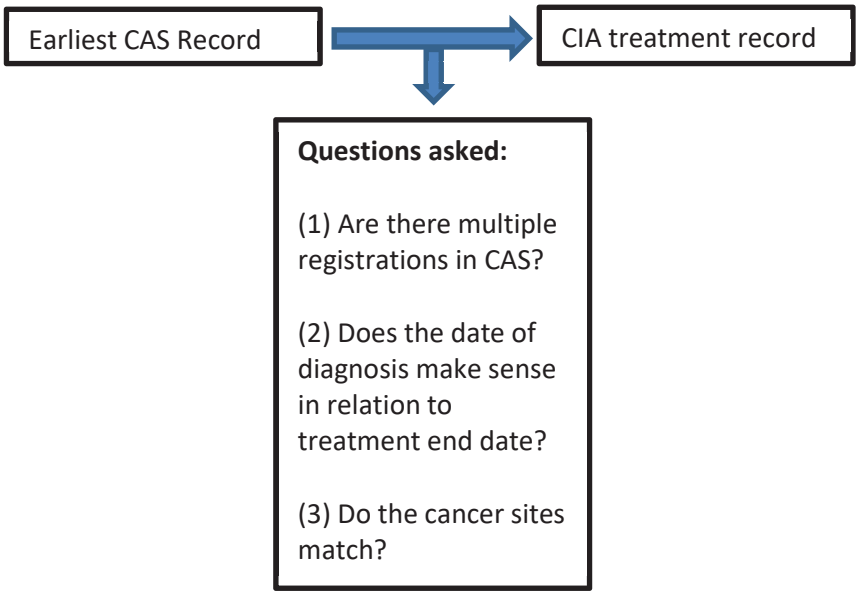
  1. Identify which and how many CIA patients have no matches with the CAS data whatsoever

  2. Identify CIA patients who have CAS records prior to their CIA records and determine which of these refer to a cancer that occurred prior to the cancer treated in the CIA data. These patients would be excluded from my study, unless the prior records are benign, carcinoma in situ of the cervix, or non-melanoma malignant skins.

  3. Identify records in the CAS for cancers that occurred after the CIA treatment record and do not refer to the same cancer. Most of these in the CAS will be second primary cancers (a few recent ones may be recurrences). Also, determine tumour IDs for CIA patients that are to be included in the study (useful for step 4).

  4. Once a final set of eligible CIA patients has been determined, using tumour IDs where possible, merge CIA data for these patients with the relevant items in CAS (the list of variables is in our study protocol).
- As a first step, the earliest record (that with the earliest diagnosis date) in CAS is merged with the record that has a matching NHS number in the CIA data. A tag is also created for

those records in CAS that have multiple registrations. Based on this tag, patients were segmented into different types of merge, based on whether they have multiple or single CAS registrations, and on whether the earliest CAS registration matches in terms of date of diagnosis and cancer site with the CIA treatment record:



- Below is the breakdown of types of records in CIA/CAS, in terms of single and multiple registrations and in terms of inconsistencies of dates and cancer sites. The assumption was made the assumption that diagnosis and treatment dates may not be entirely accurate, and so a diagnosis date was allowed to have occurred up to two years before the *end date* of radiotherapy treatment, or for a diagnosis date to occur within one year after the end date of radiotherapy treatment. Any record lying within this three-year period is considered to be consistent in terms of dates. Sites had to be exact matches.

Single or multiple records in CAS	**Type of inconsistency (Date or Site)**	**Number**	**Percent of total**
Single	None	17,443	74
Single	Site does not match	1,360	6
Single	Date does not match	614	3
Single	Date and site do not match	68	0
Multiple	First record matches fully (*must investigate later records for potential second cancers*)	1,965	8
Multiple	First record date matches, site does not	416	2
Multiple	First record site matches, but date of diagnosis much earlier than treatment dates in CIA	1,267	5
Multiple	First record site matches, but diagnosis date comes a year or more after treatment dates	1	0
Multiple	First record site does not	566	2

	match, diagnosis date much earlier than treatment dates		
Multiple	First record site and dates do not match	1	0
Multiple	(at least one record 2013+)	4	0
Total		**23,705**	**100**

- If the sites of the first record did not match, the CIA and CAS records were compared manually in order to see whether these were similar enough to be considered the same cancer (eg. rectum and rectosigmoid junction or invasive breast cancer and DCIS). In most cases, it was assumed that the CAS record had the correct site and used that; but in cases where the CAS site would not plausibly have led to high-dose radiotherapy, the CIA site was chosen (eg colon and rectum). (Patients with a mismatch of colon and rectum cancer sites are dropped, as well as invasive breast cancer/DCIS later on).
- Multiple cancers could have happened before their radiotherapy treatment record or afterwards. A next step was to sort out which patients to exclude from the study as having had a prior cancer, which records to remove as they are most likely duplicate or erroneous records, and which patients to censor at a second cancer that happened after their radiotherapy treatment. Once this work was complete, it was possible to identify which tumour IDs in CAS to retain, to conduct a full merge with the CAS data.
- When sorting those with multiple records, if multiples appeared to be erroneous duplicates, then the first or complete/more coherent record was kept. If multiples appeared to be genuine records, a second cancer was defined as (a) one which occurred at a different site in the body and at least 30 days after the diagnosis of the first tumour OR (b) one which occurred at the same site in the body at least 365 days after the diagnosis of the first tumour (except for contralateral breast cancer, which fell into category a). Patients with different tumour sites within 30 days were removed, as they had multiple primaries too close together. If patients had same tumour sites within one year of diagnosis, these were first double-checked in CAS and then dropped. See RebCheckMergeCIA_CASprelim1.xls in which Rebecca Girdler went through the records to check and most are entirely dropped unless contralateral BC (variable in do-file is rebcheck).
- If any record was determined to be an event, then any subsequent records were ignored, as patients were to be censored at the first event.
- Slight differences in site were checked manually and if similar enough, CAS site presumed to be correct in most cases, unless RT not possible for CAS site but possible for CIA site (then CIA site kept).
- Most recent data outputs: MergeCIA_CASprelim_5May2015.dta (full data, N=20,813) and ToMerge_FullCAS_5May2015.xls (N=**20,813**)

9. Pilot_CASmerge

- 27 March, 2015
- In order to test how the merge with the full CAS data would work, it was decided to test this first with a subsample of 115 patients, randomly selected with equal chances of selection by cancer site and over-sampled if they had second cancers (as these patients were thought to have more complex records to merge).

- The data report DataReport_20150430.doc describes what this do-file does, and it also describes in some general terms how CAS extracts are done. (Also see CASextractmethods.doc).
- The pilot merge aimed to test the process of bringing together the following sources of data held in the ENCORE system:

(1) CAS data with information on the tumour and its treatment, demographic information, and death information (from ONS, available through CAS)
(2) Comorbidity information
(3) HES data
(4) NCDR data (old cancer registry data, which we did not end up using, as we could use CAS data instead)

- These datasets themselves are separated into tables of information that must be linked via one ID or another in order to get the information all in one place (some contain patient IDs, some tumour IDs, others NHS numbers). As this is a rather complex process, we decided to pilot this process before conducting the merge with all 20,813 individuals.
- The first step was to ascertain whether any new cancers had been reported. This was done by extracting all information from the ENCORE system for the NHS numbers of patients we had identified. This meant that we extracted at least one, but in some cases multiple tumour IDs, per patient. The tumour IDs were then merged back to the original dataset that were appended together in step number 7 above. Any tumour IDs that did not match would then be new records that were previously in the dataset (these could be new primary cancers or they could be corrected tumour records assigned new numbers). In this pilot merge, there were no new tumour IDs.
- All tables that were linked up within ENCORE contained one record per tumour ID other than the table containing treatment information. For this table, there was an average of four records for each individual in the pilot. In order to deal with this multitude of records, a separate programme was needed to deal with these records in long form first, before making them wide to merge into the rest of the data (see CASPatientTreatDM .do below).
- Most recent data outputs: Pilot_CASmerge_10Apr2015.xls (N=114)

10. PilotMergeBack

- 14 April 2015
- Merges pilot CAS extract with original appended CAS extract (AppendCAScleanWithMults_26Jan2015.dta)
- Most recent data outputs: None. This was just a testing file to see whether merge would work.

11. PilotTreatmentMerge_manage

- 1 May 2015
- Initial exploration of treatment data for pilot patients.
- No output.

12. MergedCAS_DM

- 15 May 2015

- This file manages data from a full extract of IDs from CAS, following on from the pilot above. Once the identifiable data and date variables have been formatted for Stata usage and a few duplicates dropped, the data are merged to the latest data file merging initial CAS and full CIA data (MergeCIA_CASprelim_5May2015). These data are then further managed, including the creation of suffixes to indicate the source dataset of each variable, and the creation of anonymised variables that can be sent to CTSU. As part of this do-file, the treatment data are also merged in, after running a treatment data management programme (step 13 below).
- Most recent output: MergedCAS_CIA_TRT_18Nov2016.dta (N=**20,643**)

13. CASPatientTreatDM

- 8 June 2015
- The treatment data involves up to 37 lines of data per any patient, as they could have multiple forms of treatment. The treatment data held in CAS come in directly from hospitals and appear to be "relatively good" – ie, no one has no records of treatment, though many records are of unknown type. In order to make the data possible to analyse as one line per patient, records are sorted in this programme by date and tagged as numbers 1-37. These are then turned into a wide dataset on tumour ID. Initially data of identical treatment code on any given date (eg "cytotoxic chemotherapy" or "curative surgery") were removed, so as to produce fewer wide variables. However, this do-file was significantly amended 18 November 2016 to bring back in all the previously removed lines of treatment data, as counts of chemotherapy and other treatments may be helpful for analysis.
- Most recent output: CASPatientTreatDM_18Nov2016.dta (20,768 – but the file in 12 above comes after this)

14. PalliativeCIACheck

- 20 September 2015
- Once all the patients had been selected as eligible, it was necessary to ensure that none of them had received any prior palliative radiotherapy as per the original CIA dataset. This programme merges the latest run output from step 12 (MergedCAS_CIA_TRT_10Sep2015.dta at the time) with the original CIA file including all patient records (CIASEelig_17Jun2014.dta). Any records with fewer fractions are examined to see whether patients might have had prior radiotherapy and should be excluded. Only 14 records are identified. These were removed from the study.
- Most recent output: None. Patients are dropped in MergedCAS_DM.do.

15. RandomIDs

- 18 June 2015
- This programme generates a random set of N IDs in the range of 200,000 to 400,000, based on a fixed seed. N is the total number of patients in the dataset that is to be transferred to CTSU for anonymised analysis. Also, a set of IDs in the range of 600,000 to 800,000 is created as event identifiers.
- Most recent output: RandomIDs_10Sep2015.dta

16. Anonymisation

- 17 June, 2015
- This file drops all identifiable variables (and some other not useful ones), merges in the random IDs created in step 16 and saves an "unlock" file with the random and true identifiers.
- Most recent output: MergedCAS_CIA_TRTanon_10Sep2015.dta

17. TestLinkCWT

- 24 June 2015
- This file keeps a subset of identifiers to send to the West Midlands for PHE colleague Carolynn Gildea to merge in Cancer Waiting Times data.
- The purpose of looking at Cancer Waiting Times data is to use the variable ca_trt_event_type_code, which codes events as one of the following:
    - First definitive treatment for a new primary cancer
    - Second or subsequent treatment for a new primary cancer
    - Treatment for a local recurrence of a primary cancer
    - Treatment for a regional recurrence of cancer
    - Treatment for a distant recurrence of cancer (metastatic disease)
    - Treatment for multiple recurrence of cancer (local and/or regional and/or distant)
    - First treatment for metastatic disease following an unknown primary
    - Second or subsequent treatment for metastatic disease following an unknown primary
    - Treatment for relapse of primary cancer (second or subsequent)
    - Treatment for progression of primary cancer (second or subsequent)
- Most recent output: TestLinkCWT_24Jun2015.dta and TestLinkCWT_24Jun2015.xls

18. MergeCore_CWT

- 15 September 2015
- After some initial formatting and data management of just Cancer Waiting Times data, these are merged with the CAS and CIA data. There are many multiples in the CWT data. These are sorted in terms of date and some are initially dropped, if treatment types are uninformative (same type of treatment again, for instance). Others are sorted by date, to be examined in waves by date. Initially the earliest record is kept in a merge with the CAS/CIA record and grouped in terms of match by date and cancer site. Records are examined in groups by whether they are metastases/recurrences, or whether they are treatments for primary cancers. These are then either deemed matches for first treatments of primary cancers (records not of interest, as these data are already available), records showing treatment much before CAS/CIA data for this patient (requiring throwing out of these patients – only few), and designation as outcome of interest – either recurrence or metastasis, or second primary cancer. If a patient is already deemed to have a second primary cancer, dates are compared to see whether CWT record came first and should replace the second primary cancer record in CAS.

- Most recent output: This progamme is not complete, because we stopped the use of CWT data. Recurrence is most important in breast patients, and the national algorithm developed by Gurdeep Mannu et al is better than use of CWT data (which are only one source of information, and this variable of interest is only available from 2009 onwards).

19. GenSiteGpCWT

- This is part of step 18 and groups cancer sites into the same numeric groups used elsewhere in CAS and CIA. No output file.

20. RebNewCASextract

- 14 September 2016
- Using the most recent run of MergedCAS_DM.do at the time (MergedCAS_CIA_TRT_3Feb2016.dta), this programme extracts a list of identifiers so that all information for these NHS numbers can be pulled out of CAS for a CAS update.
- Most recent output: RebNewCASextract_20161007.dta/ RebNewCASextract_20161007.xls (N=22,673, includes second cancers)

21. CAS_UpdateRedo

- 8 November 2016
- To create a final analysis dataset, it was decided to update CAS data so that any new second primary cancers, any data error corrections, and especially updates in vital status could be incorporated into the analysis. In order to update CAS data, the following steps needed to be taken:

(1) Retrieve all records from CAS for all tumour IDs still included in the most up to date dataset currently in use (MergedCAS_CIA_TRT_3Feb2016.dta)
(2) Merge these data onto the raw CAS extract appended together in step 7 above. All records that match the original CAS extract can be ignored, as these were already dealt with in earlier work. Any non-matching data needed to be checked: records only in the old CAS dataset were errors and replaced with new records in the updated CAS (these needed to be replaced in my dataset also). Any records only available in the new CAS were either corrected records for non-matches in the old CAS or they were new records of second primary cancers that needed to be incorporated for analysis.
(3) Once records had been corrected and new second primary cancers identified, a new set of tumour IDs was obtained and all data for these extracted from CAS.
(4) Tumour records for second primary cancers then needed to be merged in wide to the first primary tumour record.
(5) This updated CAS dataset then needed to be merged back to the CIA data.

- This programme does steps numbers 2-3.
- Most recent data outputs: CAS_Update_20161102_1Dec2016.dta, IDsForFinalCASmerge_1dec2016.dta, IDsForFinalCASmerge_20161123.xls(N=22,025, includes second cancers)

22. IMD

- 9 January 2017

- This programme has two purposes: it creates a population-based IMD quintile variable based on the raw IMD information using lower super output areas in each of the relevant IMD score files available: 2004, 2007, 2010, and 2015.
- The programme then groups patients in my study by date of entry, using guidelines provided by PHE: patients entering the study between 2000 and 2002 are mapped onto IMD 2004 data, patients entering between 2003 and 2006 are mapped onto IMD 2007 data, patients entering between 2007 and 2010 are mapped onto 2010 data, and patients entering in 2011 or 2012 are mapped onto 2015 data. See Appendix 4 that describes how PHE uses each of the IMD datasets (2004, 2007, 2010). In addition, here are the websites with data and descriptions for 2010 and 2015 data: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 and https://www.gov.uk/government/statistics/english-indices-of-deprivation-2010 . Websites for 2007 and 2004 data are not openly available, and these data were obtained through PHE.
- Both IMD quintile information and raw IMD scores are prepared for a merge with CAS (see 23 below).
- Most recent output files: LSOAs2007_10Jan2017.dta, LSOAs2010_10Jan2017.dta, LSOAs2015_10Jan2017.dta, LSOAs2004_10Jan2017.dta, IMD2004_10Jan2017.dta, IMD2007_10Jan2017.dta, IMD2010_10Jan2017.dta, IMD2015_10Jan2017.dta

23. MergedCAS_DM_UPDATE

- 1 Dec 2016
- This programme imports updated CAS data into Stata, manages data formatting, and then continues on with step 4 listed in 21 above. Second primary cancer records are removed and merged back in wide on NHS number, after being identified as being second primary cancer information (variables suffixed with "_2R").
- In addition, some old CAS information is merged back as reference. Note that previously cancer site information was changed for very similar cancer sites between CIA and CAS data. Now this information is replaced for invasive breast and DCIS sites, rather these are labelled as differing between the two. All patients diagnosed as colon cancers in CAS are also removed.
- Updated treatment information is then brought in (see 24 below). Also brought in is separate RT only information, which is contained within the treatment information but separating this out makes it easier to compare RT CAS information with RT CIA information later (see 25 below).
- Additional Leicester NSCLC patients are also added in (see 26 below).
- Second cancers arising in 2015/2016 are also brought in (see 27 below) as well as a few new embarkation dates.
- Next, variables for anonymisation are created, some of which are also used for survival analysis.
- Finally, IMD quintile and raw score variables are merged in using LSOA 2001 for IMD 2004, 2007, and 2010 information, and LSOA 2011 for IMD 2015 information (see 22 above).
- Most recent output file is MergedCAS_CIA_TRT_UPDATE_27Jul2017.dta. (N=20,381)

24. CASPatientTreatDM_UPDATE

- 1 Dec 2016
- This programme imports updated CAS treatment data into Stata, manages data formatting and then prepares data for merge with other CAS data. This is done by making the dataset wide based on the date of each treatment event for each patient. Formerly, similar records were dropped if they occurred on the same date, but these are now kept in.
- Most recent data outputs: CASPatientTreatDM_UPDATE_3Apr2017.dta, CASPatientTreatDM_UPDATELONG_3Apr2017.dta (for data checks only), CASPatientTreatForRT_3Apr2017.dta (input for 25 below)

25. CASPatientTreatDM_UPDATE_RT

- 1 Dec 2016
- This programme imports updated CAS treatment data into Stata, manages data formatting and then prepares data for merge with other CAS data. This is done by making the dataset wide based on the date of each treatment event for each patient. Formerly, similar records were dropped if they occurred on the same date, but these are now kept in.
- Most recent data output: CASPatientTreatDM_UPDATE_RT_16Mar2017.dta

26. LeicesterNSCLCPatients

- 17 January 2017
- This programme adds 12 patients from later Leicester data to my dataset, in order to increase my NSCLC sample.
- Most recent data output: LeicesterNSCLCPatients_18Jan2017.dta (N=12)

27. SecondCancers1516

- 26 May, 2017
- In this programme additional second cancers, obtained in the March 2017 CAS snapshot for the years 2015 and 2016, are added. Note that this is probably only up to date to end of March, 2016, so there will be some missing events after this. For the purposes of invasive breast cancer analyses, use cut-off date for analyses end April, 2017, as there is one event on 4th April I don't want to miss.
- Most recent data output: SecondCancers1516_26May2017.dta, N=202

28. DataPrep

- 6 October 2016
- Further data cleaning. Removing remaining NSCLC patients with fewer than or equal to 15 fractions (as cannot tell if these are palliative, N=5). Removal of invasive breast/DCIS patients who drop out of analyses due to not meeting criteria for recurrence algorithm (N=71).
- Also, removal of patients whose CAS treatment records show prior radiotherapy (N=191). And removal of invasive breast, DCIS, and NSCLC patients whose RT came more than a year after cancer diagnosis (N=413).

- Correction and addition of information for Oxford NSCLC patients based on NSCLC patient notes project (N=126).
- Correction of start dates and/or replacement of missing start dates with dates in CAS treatment information, if these make sense with finish dates in CIA.
- Creation of variables for analysis: age, NSCLC group, other treatment information, laterality, morphology, survival analysis outcome and time-to-event variables, EQD2T
- Removal of invasive breast patients who had mastectomy and received boost (N=43)
- Most recent data output: DataPrep_16Aug2017.dta (N=**19, 654**)