Hyperfractionated/accelerated radiotherapy regimens for the treatment of non-small cell lung cancer.
A systematic review of clinical and cost-effectiveness

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WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION

The WMHTAC produces rapid systematic reviews about the effectiveness of health care interventions and technologies, in response to requests from West Midlands Health Authorities. Reviews take approximately 6 months and aim to give a timely and accurate analysis of the available evidence, with an economic analysis (usually a cost-utility analysis) of the intervention accompanied by a statement of the quality of the evidence.

CONTRIBUTIONS OF AUTHORS

Beverley Wake was the main author and was responsible for the day to day management of the report; undertook searches; designed the protocol; designed and piloted data inclusion, data extraction and study quality proforma; undertook assessment of study eligibility, validity and extracted and collated data from them; liased with experts and wrote and collated the report.

Rod Taylor was the project manager and took overall responsibility for the report. He advised on protocol development and writing of the report; checked data extraction; wrote some of the section on the cost-effectiveness and provided general advice.

Josie Sandercock carried out statistical analysis of survival data and provided general statistical advice

All the named authors commented on, and agreed the final version of this report.

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Anne Fry-Smith	Advice on search strategies
Christine Leonard	Administrative assistance
Cindy Billingham	Advice on Quality of Life data

West Midlands Health Technology Collaboration Recommendation:

The recommendation for the preferential use of accelerated radiotherapy alone or with chemotherapy over standard therapy is:

NOT SUPPORTED

The recommendation for the preferential use of hyperfractionated radiotherapy alone or with chemotherapy over standard therapy is:

NOT SUPPORTED

The recommendation for the preferential use of hyperfractionated, split-course radiotherapy alone over standard therapy is:

NOT SUPPORTED

The recommendation for the preferential use of hyperfractionated, split-course radiotherapy with chemotherapy over standard therapy is:

SUPPORTED LEVEL II

The recommendation for the preferential use of Continuous Hyperfractionated Accelerated Radiotherapy (CHART) over standard therapy is:

STRONGLY SUPPORTED LEVEL I

Anticipated Expiry Date

- This report was completed in January 2002.
- The searches on clinical effectiveness were completed in November 2001, searches on cost-effectiveness in November 2001.
- One trial is currently ongoing on the use of CHARTWEL in NSCLC and it is anticipated that this trial will provide essential information to support the use of this type of regimen, and is likely to be more practical for application in the NHS. The trial is still recruiting and therefore we do not anticipate results to be available until at least 2006.
- On reporting of the results from this trial it is anticipated that this report require updating.

EXECUTIVE SUMMARY

Background

- This systematic review was undertaken to address a regional policy question regarding the clinical effectiveness and cost-effectiveness of non-conventional radiotherapy regimens i.e. hyperfractionated, accelerated and combined hyperfractionated/ accelerated radiotherapy regimens (with or without adjuvant chemotherapy) in comparison to conventional/standard radiotherapy regimens for patients with inoperable non-small cell lung cancer (NSCLC) since it was perceived by the medical community that there may be a survival advantage with non-conventional regimens (particularly CHART-Continuous Hyperfractionated Accelerated Radiotherapy).

- The median survival of NSCLC patients treated with standard radiotherapy alone is approximately 10 months or less, with a 5-year survival rate of 5-10%, and there is a high service need since there are approximately 800 eligible cases a year in the West Midlands Region for this therapy. The review therefore aimed to assess the clinical effectiveness of such regimens. Since the introduction of such regimens may be associated with increased costs to the NHS, cost-effectiveness was also reviewed.

- The rationale behind hyperfractionation is to exploit the enhanced repair capacity of dose-limiting, late-reacting, normal tissues compared with rapidly proliferating tumour cells, while the aim of acceleration is to minimize the potential for tumour cell repopulation during treatment. However, in practice, total dose may be reduced because acceleration can lead to increased acute effects[1,2].

Clinical Effectiveness

- Seven trials[2-8] varying considerably in size were identified covering 7 different regimens and there were only two regimens where more than one study provided data. The quality of the trials varied from poor to good and there was a lack of information on the blinding of outcome assessors, however as in many cancer trials the blinding of assessors may not have been practicable. This may not be of great relevance when measuring survival but may introduce bias into the measurement of other outcomes. The quality of the CHART paper was good while the trial reporting a statistically significant survival advantage for the split-course, hyperfractionated radiotherapy with chemotherapy regimen[8] was relatively poor and supplied little data on adverse events.

- Two regimens were found to have a statistically significant overall survival advantage; CHART, which included the results from one large good quality (562 patients) trial[2] (Hazard Ratio 0.78 95% CI 0.66-0.94) and split-course, hyperfractionated radiotherapy with chemotherapy where the results from two[4,8] smaller, poorer quality trials (126 patients overall) were pooled (Hazard Ratio 0.48 95% CI 0.33-0.7). There did not appear to be increased incidence of adverse events in either of these regimens although in one trial[8] this was badly reported. Quality of Life was studied for the CHART regimen[9] and there was shown to be significantly more pain on swallowing and heartburn, however this was only in the short-term.

Cost Effectiveness

- No formal cost-effectiveness studies were identified although there were two[10,11] cost-impact studies. One[10] assessed the costs of CHART vs standard radiotherapy in NSCLC in the UK, while the other[11] provides the costs of various management and treatment strategies for NSCLC in the UK. Utilising assumptions based on the generalisability of costs identified above and the patterns of service delivery, we concluded that all non-conventional regimens studied (except accelerated regimens alone) are likely to be associated with a cost increase of up to £3000, per patient, per year.

- The cost per LYG for split-course, hyperfractionated radiotherapy with chemotherapy was £2311 (£1231 to £5778) and for CHART £11,227 (£6062 to £50,520). Therefore both these regimens are likely to be cost-effective. Importantly this estimate does not include QoL data only survival (since QALYs could not be calculated from the CHART QoL study[9]) and the costs of potential adverse events associated with chemotherapy and the radiotherapy was not available.

Other implications for the NHS

- As well as a cost-impact on the NHS a change to the use of the CHART regimen requires a change in working practices and is likely to have associated increases in costs, 'out of hours' use of staff and hospital beds may be required although weekend-less regimens may reduce these costs. A switch to any 'new' regimen is also likely to be associated with increased costs.

Implications for other parties

- The lack of quality of life (QoL) data is a very important issue, however for CHART where this was available, there were only significant disadvantages over standard treatment in the short term (during treatment and in the few weeks after), therefore it is possible that patients would be willing to suffer short-term effects to gain a survival advantage. This cannot be substantiated with evidence. For the split-course, hyperfractionated regimen with chemotherapy no QoL data is available and adverse events were poorly reported. Since this regimen includes chemotherapy and takes longer to complete than the CHART regimen it is possible that the CHART regimen may be preferable to patients. Although CHART may be associated with inconvenience on behalf of patients and carers, the short-term nature of this treatment may also make it favourable. Again this cannot be substantiated with evidence.

Implications for further research

- Results from the CHARTWEL (CHART weekend-less) trial[12] may prove useful in the future as it may be associated with less inconvenience for patients and carers and less problems in changing policy for the NHS but it necessary to stress that a QoL study making it possible to calculate QALYs and a well carried out cost-effectiveness study would be particularly useful in this area as well as for the split-course, hyperfractionated regimen with chemotherapy. For the other regimens in this review the same is true and more trials in those areas are also necessary.

ACRONYMS AND ABBREVIATIONS

5-FU	5-fluorouracil
Ac	Adenocarcinoma (type of NSCLC)
ACC-RT	Accelerated radiotherapy
CA	Cancer
CDBCA	Carboplatin (platinum analogue)
CHART	Continuous hyperfractionated accelerated radiotherapy
CHARTWEL	Continuous hyperfractionated accelerated radiotherapy weekend-less
Cost/LYG	Cost per Life Year Gained
CP	Cyclophosphamide
CT	Chemotherapy
Dx	Disease
ECOG	Eastern Co-operative Oncology Group
HA	Health Authority
HFX-RT	Hyperfractionated radiotherapy
HR	Hazard Ratio
KPS	Karnofsky performance status
n/a	Not applicable
N/S	Not stated
NSCLC	Non-small cell lung cancer
QALY	Quality Adjusted Life Year
O-E	Observed – Expected
QoL	Quality of Life (data)
RCT	Randomised controlled trial
Rx	Treatment
SCLC	Small cell lung cancer
SCHFX-RT	Split-course, hyperfractionated radiotherapy
STD-RT	Standard/conventional radiotherapy
V	Varience
VP-16	Epipodophyllotoxin etopside
WHO-PS	World Health Organisation Performance Status

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1. AIM OF REVIEW

In England and Wales lung cancer is responsible for approximately 20% of all cancer deaths and around 5% of all deaths in England and Wales each year[13]. The conventional radiotherapy treatment for inoperable non-small cell lung cancer is relatively ineffective in increasing survival in these patients and so alterations in the radiotherapy regimen have been adopted in many centres. They generally involve using more fractions daily (acceleration) and these fractions are often smaller than conventionally used (hyperfractionation). This report has been undertaken in response to a regional request for advice on the potential implementation of CHART (continuous Hyperfractionated accelerated radiotherapy) and CHART-like regimens for the treatment of inoperable non-small cell lung cancer. CHART involves both of these alterations which are administered continuously i.e. continuous hyperfractionated accelerated radiotherapy. This report systematically reviews the clinical effectiveness and cost-effectiveness of hyperfractionation, acceleration and combined hyperfractionation/acceleration radiotherapy regimens (with or without adjuvant chemotherapy) in comparison to conventional treatments for patients with inoperable non-small cell lung cancer.

2. BACKGROUND

2.1 DESCRIPTION OF UNDERLYING HEALTH PROBLEM

Lung cancer is a major source of mortality in England and Wales and indeed the developed world where 80-90% of cases are related to smoking[14]. In one study of life-long smokers, the cumulative risk of lung cancer at age 75, was 15.9% for men and 9.5% for women[15]. Regional figures for the West Midlands show that at present there are around 3000 deaths per year from lung cancer (male:female ratio of approximately 2:1), giving a crude death rate of approximately 60 per 100,000 population. The figure is highest in males (approximately 80 per 100,000) although it appears to be on a steady decline while the figure for females remains steady (approximately 40 per 100,000). The crude incidence rate is approximately 65 per 100,000 per year, therefore in the West Midlands (5.3 million) there will be 3445 new cases per year. These figures are not thought to vary from those at a national level[16].

Lung cancer is divided into 2 main histological groups, small cell lung cancer (SCLC) making up approximately 20% of cases and non-small cell lung cancer (NSCLC) being approximately 80% of cases[14]. Non-small cell lung cancers are further divided into 3 main types (see appendix 1) ; squamous cell lung cancer which is at present the commonest type in Europe, being generally slow growing and late to metastasize; adenocarcinoma which is more aggressive and fast spreading; large cell carcinoma with a similar behaviour to adenocarcinoma[14]. It appears that squamous cell carcinoma is on the decrease relative to adenocarcinoma which is on the increase both in North America and Europe[17]. The reasons for the shift are unknown.

Approximately 2756 (80% of 3445) new cases of NSCLC are diagnosed every year in an average HA, of these around 25%[18] (861 cases) will present with stage I/II disease (see appendix 1 for staging details), which is generally surgically resectable. The majority of patients present with advanced stage (III/IV) disease. It can be assumed that around 40-50% of new cases of NSCLC will have metastatic disease (stage IV) which is unsuitable for curative treatment. Of the remaining 25-35% patients presenting with stage III disease a small

proportion may be suitable for surgical resection whilst the remaining patients may be suitable for radio or chemotherapy[14].

Since some early stage patients may be medically unsuitable for surgery we make the assumption that approximately 25-35% of patients presenting with NSCLC may be suitable for potentially curative treatment with a radiotherapy regimen, this equates to around 861-1206 (25-35% of 3445) new cases per year in the West Midlands region.

Stage IIIB patients are most likely to be treated with curative radiotherapy, however most patients will have early progression of their disease due to the presence of undiagnosed micrometastatic disease at the time of diagnosis. The median survival of patients treated with radiotherapy alone is approximately 10 months or less, with a 5-year survival rate of 5-10%.

2.2 CURRENT SERVICE PROVISION

The usual current treatment in the region for inoperable NSCLC which is not yet widespread is described as 'conventional or standard radiotherapy'. This is commonly a total dose of 50 Gy in 15 fractions over 3 weeks or 55 Gy in 20 fractions over 4 weeks (Birmingham) or 64 Gy in 32 fractions over 6/12 weeks (National). Worldwide the most commonly used regimens employ fraction sizes of 1.8 -2.0 Gy, given daily Monday to Friday to a total dose of 60 – 70 Gy[1]. Alternatively therapy may be given in 2 doses the first targeting a large area including lymph nodes and the second targeting the primary tumour directly.

2.3 DESCRIPTION OF INTERVENTIONS UNDER EVALUATION

The interventions to be considered in this review are any radiotherapy regimens which can either be described as hyperfractionated, accelerated, or both. These radiotherapy regimens may also use adjuvant chemotherapy. Standard radiotherapy may also be combined with chemotherapy, however this regimen was not considered in this review. The CHART regimen[2] was first adopted in 1985 at Mount Vernon Hospital in Middlesex and requires the use of many small fractions given over a reduced time. The rationale behind hyperfractionation is to exploit the enhanced repair capacity of dose-limiting, late-reacting, normal tissues compared with rapidly proliferating tumour cells, while the aim of acceleration is to minimize the potential for tumour cell repopulation during treatment. However, in practice, total dose may be reduced because acceleration can lead to increased acute effects[2],[1].

Table 1 - Definitions and reasoning behind the use of various radiotherapy regimens

Radiotherapy Regimen	Definition and reasoning
Accelerated	The use of two or more fractions of standard fraction size daily to the same conventional total dose as standard radiotherapy, increasing the number of fractions per week and shortening the overall treatment time. The intent of accelerated radiotherapy is to reduce re-population in rapidly proliferating tumours. Acute normal tissue toxicity is usually increased.
Hyperfractionated (non-accelerated)	The use of two or more fractions daily of smaller than conventional fraction size. This results in an increased total nominal tumour dose compared with standard radiation. The rationale is to exploit the enhanced repair capacity of dose-limiting, late-reacting, normal tissues compared with rapidly proliferating tumours.
Hyperfractionated Accelerated	Combines the features of the two regimens described above i.e. the use of two or three fractions of smaller fraction size daily delivered over a shorter period of time then conventional therapy. The rationale is to reduce long-term normal tissue toxicity by smaller fraction size and to reduce the risk of re-population in rapidly proliferating tumours. Variants include Continuous Hyperfractionated Accelerated Radiotherapy (CHART) and Continuous Hyperfractionated Accelerated Radiotherapy Weekendless (CHARTWEL).
Split-course	Originally designed to diminish radiation morbidity by splitting the total dose into at least two separate courses with an interruption of 10 to 14 days. Most radiation oncologists consider split-course radiotherapy to be disadvantageous compared with continuous treatment because the decreased radiation morbidity of normal tissues will also result in lower anti-tumour efficiency and reduced local control rates. There is also concern about repopulation during the rest period.

A change to the use of such regimens requires a change in working practices and is likely to have associated increases in costs[1], 'out of hours' use of staff and hospital beds may be required although weekend-less regimens may reduce these costs. Therefore the important consideration is whether the clinical effectiveness of such regimens (if a significant benefit over treatment with conventional treatments is concluded) outweighs the potential increase in costs and the change in working practice.

2.4 POLICY QUESTIONS TO BE ADDRESSED BY THIS REVIEW

In patients with inoperable non small cell lung cancer, to assess the evidence base for the clinical effectiveness and cost effectiveness of:

(a) Accelerated radiotherapy (alone or in combination with adjuvant chemotherapy) versus standard radiotherapy.

(b) Hyperfractionated radiotherapy (alone or in combination with adjuvant chemotherapy) versus standard radiotherapy.

(c) Hyperfractionated, split-course radiotherapy (alone or in conjunction with adjuvant chemotherapy) versus standard radiotherapy.

(d) Combined hyperfractionated/accelerated radiotherapy (CHART) (alone or in combination with adjuvant chemotherapy) versus standard radiotherapy.

This review did not include standard radiotherapy with chemotherapy as it was not determined to be an important policy question. However this review cannot therefore comment conclusively on whether regimens with chemotherapy are better because of the radiotherapy regimen or the chemotherapy since there is no control for this comparison.

3.0 CLINICAL EFFECTIVENESS

3.1 METHODS

3.1.1 SEARCH STRATEGY

A broad comprehensive search for primary studies assessing the clinical effectiveness of these 'non-conventional' radiotherapy regimens was undertaken involving:

- Electronic bibliographic database searches ; **MEDLINE** (Ovid) 1966-November 2001; **Embase** (Ovid) 1980-November 2001; **CANCERLIT** 1966-November 2001 **Cochrane Library 2001** Issue 3 (see Appendix 2 for detail on search terms used)
- Citation checking of studies and reviews obtained
- Contact with experts in the field (see Appendix 3 for list)
- Internet search engines including lycos, excite and netscape using terms such as 'non-small cell lung cancer' and 'radiotherapy' and specific terms such as 'hyperfractionated' and 'accelerated'.
- There were no language restrictions.

3.1.2 INCLUSION AND EXCLUSION CRITERIA

The following inclusion and exclusion criteria were applied to all identified studies by BW and a 20% sample checked by RT for agreement. A 'kappa' score of 0.81 (SE=0.13) was calculated to detect interrater agreement (i.e. Kappa ranges from 0-1) and showed there was good agreement between the two reviewers on which studies should be included and which

excluded. For those studies where this could not be decided on abstract alone references were obtained in full.

- **Intervention**: The intervention must be a non-conventional radiotherapy regimen based on hyperfractionation or acceleration or both. Adjuvant chemotherapy was admissible.

- **Population**: Patients must be adults with non-small cell lung cancer which is inoperable but not yet widespread (i.e. not stage IV). Generally such patients will be stage III, however studies were also included if patients had a lower stage of disease (i.e. stages I, II and III) if they were considered unsuitable for surgical resection for any other reason i.e. patients who would clinically be considered for this treatment

- **Comparator**: The comparator must be considered to be a standard radiotherapy regimen as used in the UK i.e. approximately 2Gy fractions given once daily to a total of 60-70Gy. Since adjuvant chemotherapy is not current practice a combined radiotherapy/chemotherapy regimen was not considered to be 'conventional/standard' treatment i.e. current service provision.

- **Outcomes** : The primary outcome was survival. Secondary outcomes were adverse events, quality of life and clinical response.

- **Study design** : Searches were limited to identify randomised controlled trials (an experimental study design where patients are randomized into either control or study groups. The control group generally being current or existing treatments or no treatment, which may be a placebo in terms of a drug trial, and the study groups being the 'new' intervention/s to be considered). Initial scoping searches revealed several randomised controlled trials to be available.

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3.1.3 DATA EXTRACTION STRATEGY

Data concerning study characteristics, study quality and results were extracted by BW and checked by RT using a series of standard data extraction proforma (Appendix 8). Any differences were resolved by consensus.

3.1.4 QUALITY ASSESSMENT STRATEGY

A modified version of the Jadad[19] checklist for RCTs was used to determine study quality i.e. internal validity. This included a qualitative assessment of the trial in terms of selection bias (randomisation), confounding (concealment), assessment bias (blinding of outcome) and attrition bias (intention-to-treat analysis). In addition to an item by item assessment (Appendix 4), an overall total quality score was determined for each trial.

The quality assessment was performed by BW and checked by RT and any differences resolved by consensus.

The study characteristics, quality and numerical results are summarised in tabular form according to the policy questions of this review. It was intended to perform meta-analysis where study results allowed. The desired method is to obtained figures for the Hazard ratio and its variance and present these for each trial and then combined for trials which are comparable i.e. answer each of the policy questions. In practice it may be necessary to estimate the hazard ratio and its variance[20] or from other results presented such as Kaplan-Meier survival curves (see appendix 9).

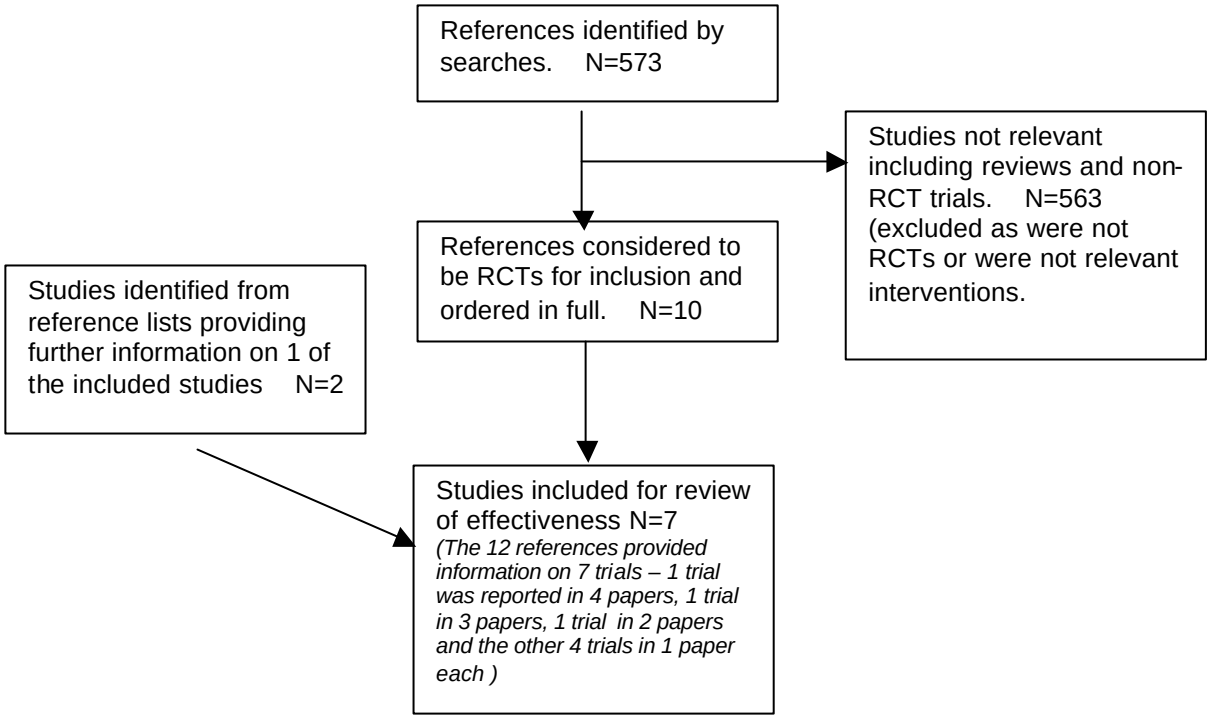
3.2 RESULTS

3.2.1 QUANTITY AND QUALITY OF RESEARCH AVAILABLE

- **Number of studies identified**

The search identified 573 studies of which 12 (see appendix 5) were considered relevant on application of the inclusion/exclusion criteria of the review. Studies clearly identifiable as reviews from the abstract were also excluded at this stage. These 12 studies were RCTs and were therefore obtained in full text for inclusion in this review.

All 12 studies were finally included, however they provided information on only 7 RCTs i.e. three of the included trials had more than one publication ; Saunders[2] had 3 publications[2,21,22], Ball[3], 2 publications[3,23] and Sause-RTOG[7] had 2 publications[7,24]. Further information on a quality of life study performed on the patients in the Saunders study was also available[25] and therefore data from this study is also included (appendix 5).



- **Included study characteristics**

Details of included trial characteristics are shown in tables 7 to 10 in appendix 10 and cover the following; general characteristics and interventions, patient characteristics, study outcomes and definitions, inclusion/exclusion criteria and other characteristics. The contribution of each trial to the policy questions of this review is summarized in the table below.

Table 2 - Contributions of the trials to review policy questions

Comparison	Number of trials	Trials	Trial arms to be compared
(a) Accelerated regimens			
ACC-RT vs STD-RT	1	Ball[3]	1 and 2
ACC-RT + CT vs STD-RT	1	Ball[3]	1 and 4
(b) Hyperfractionated regimens			
HFX-RT vs STD-RT	3	Kagami[5]	1 and 2
		Koca[6]	1 and 2
		Sause-RTOG[7]	1 and 3
HFX-RT + CT vs STD-RT	1	Koca[6]	1 and 4
(c) Hyperfractionated, split-course regimens			
SCHFX-RT vs STD-RT	1	Bonner[4]	1 and 2
SCHFX-RT + CT vs STD-RT	2	Bonner[4]	1 and 3
		Wang[8]	1 and 4
(d) Combined regimens			
CHART vs STD-RT	1	Saunders[2]	1 and 2
CHART + CT vs STD-RT	0	n/a	n/a

Notes: ACC-RT – accelerated radiotherapy STD-RT – standard/conventional radiotherapy
CT – chemotherapy HFX-RT – Hyperfractionated radiotherapy
SCHFX - split-course, hyperfractionated radiotherapy.

Table 3 - Description of radiotherapy regimens used in the included studies (rationale for categorising each regimen is given in table 1)

Study	Accelerated	Hyperfraction-ated	Hyperfraction-ated, split-course	Accelerated, hyperfraction-ated and continuous	Control
Ball[3]	60Gy in 30 fractions of 2Gy twice per day for 3 weeks.				60 Gy in 30 fractions of 2 Gy once per day for 6 weeks
Bonner[4]			60 Gy in 2 courses split by 2 week rest Each course 30 Gy in 20 fractions of 1.5 Gy twice per day for 2 weeks.		60 Gy in 30 fractions of 2 Gy once daily for 6 weeks.
Kagami[5]		71.5 Gy in 52 fractions of 1.375 Gy twice per day for 4 days per week for 6.5 weeks			65 Gy in 26 fractions of 2.5 Gy once daily for 4 days per week for 6.5 weeks.
Koca[6]		66 Gy in 60 fractions of 1.1 Gy twice per day for 6 weeks.			60 Gy in 30 fractions of 2 Gy once daily for 6 weeks
Saunders[2]				54 Gy in 36 fractions of 1.5 Gy three times daily for 12 continuous days.	60 Gy in 30 fractions of 2 Gy once daily for 6 weeks.
Sause-RTOG[7]		69.6 Gy in 58 fractions of 1.2 Gy twice daily for 6 weeks (29 days of treatment).			60 Gy in 30 fractions of 2 Gy once daily for 6 weeks.
Wang[8]			72 Gy in 2 courses split by 2 week rest Each course 36 Gy in 30 fractions of 1.2 Gy twice per day for 3 weeks.		60 Gy in 33 fractions of 1.8 Gy daily for 6 weeks (sc and lc) **or** 70 Gy in 35 fractions of 2 Gy daily for 6 weeks (ac).

(a) Characteristics of studies comparing Accelerated regimens with standard radiotherapy

Only 1 trial[3] was found in this category and compares both an accelerated regimen with standard radiotherapy and an accelerated regimen with adjuvant chemotherapy with standard radiotherapy. The trial is a multicentre randomized phase III trial and was carried out in Australia between 1989 and 1995. 208 patients were randomized and 204 assessed for response.

The standard radiotherapy regimen of 60 Gy in 30 fractions (2 Gy fractions) at 5 fractions per week for six weeks is very similar to the UK standard (see 2.2). The interventions of interest

are the accelerated regimen of 60 Gy in 30 fractions over 3 weeks and the same regimen with carboplatin (70mg/m^2/day on days 1-5).

Patients were predominantly male (77%) and aged between 40 and 79 years old. The majority of patients were stage IIIA/B (79%) and of squamous histology (64%), currently the most prevalent form of NSCLC in Europe. In terms of patient characteristics there were no significant differences in baseline prognostic factors between the 3 trial arms of interest. Patients were eligible for entry into the trial if they had inoperable NSCLC and therefore all patients are relevant to this review.

This trial reported survival and adverse events and also measured clinical response and local and distant progression. No QoL data was available.

(b) Characteristics of studies comparing Hyperfractionated regimens with standard radiotherapy

Three trials were found in this category, 3/3[5-7] comparing Hyperfractionated radiotherapy alone to standard radiotherapy and 1/3[6] comparing Hyperfractionated radiotherapy with adjuvant chemotherapy to standard radiotherapy. Two trials were single-centre trials, and one was a multi-centre trial and took place over 3 continents; Asia[5], North America[7] and Europe[6]. They were carried out between 1987 and 1992 although the dates for one trial are unknown[6]. Trials ranged in size from 36[5,6] to 490 patients[7].

The standard radiotherapy regimens in the 3 trials are comparable to each other and are similar to the UK standard regimen, with fractions of between 2Gy[7] and 2.5 Gy[5] to a total of between 60 Gy[6,7] and 65 Gy[5]. It should be noted that 65Gy in 2.5Gy fractions may give a larger biological effect that 60Gy in 2Gy fractions.

Patients were predominantly male ranging from 70%[7] to 97% male[5] and predominantly aged over 60 years although one trial[6] the median age is 57 and there are patients as young as 33 years old. The majority of patients were stage IIIA/B although this is unknown for one trial[6] and the majority of patients had NSCLC of squamous cell histology ranging from 44%[7] to 75%[6]. One trial[5] had notable differences in terms of baseline prognostic factors (stage and histology) between relevant trial arms. No data was available on baseline prognostic factors between trial arms for one trial[6]. In trials where eligibility data was available[6,7] all patients were relevant to this review.

All trials measured overall survival and adverse events, 2/3 measured clinical response[5,6] but none of the trials measured quality of life. One trial[7] performed a sub-group analysis on age and cancer histology.

(c) Characteristics of studies comparing Hyperfractionated, split-course regimens with standard radiotherapy

Two trials were identified in this category[4,8], 1/2 comparing Hyperfractionated, split-course radiotherapy alone to standard radiotherapy and 2/2 comparing Hyperfractionated, split-course radiotherapy with adjuvant chemotherapy to standard radiotherapy[4,8]. The trials were single-centre trials, one in Asia[8] and one in North America[4]. They were carried out between 1988 and 1993. Trials ranged in size from 110[4] to 126 patients[8].

The standard radiotherapy regimens in the 2 trials are comparable to each other and are similar to the UK standard regimen, with fractions of between 1.8 Gy[8] and 2 Gy[4] to a total of between 60 Gy[4] and 70 Gy[8]. For the trials comparing hyperfractionation with adjuvant chemotherapy, the chemotherapy regimes were not comparable (see table 3).

Patients were predominantly male ranging from 63%[4] to 90% male[8] and predominantly aged over 60 years although in one of the relevant arms in one trial[8] the majority of patients are aged less than 60. The majority of patients were stage IIIA/B, ranging from 86%[8] to 100%[4] and the majority of patients had nsclc of squamous cell histology ranging from 40%[4] to 63%[8]. One trial[8] had notable differences in terms of baseline prognostic factors between relevant trial arms, this was for patient age. All patients were relevant to this review.

Both trials measured overall survival, adverse events and clinical response but none of the trials measured quality of life. One trial[4] performed a sub-group analysis on cancer histology.

(d) Characteristics of studies comparing combined Hyperfractionated/ Accelerated regimens (only regimen found – CHART) with standard radiotherapy

Only 1 trial[2] was found in this category and compares CHART with standard radiotherapy, no trials were found which compared a combined regimen e.g. CHART with adjuvant chemotherapy to standard radiotherapy. The trial is a multicentre randomized trial and was carried out in Europe (incl. UK) between 1990 and 1995. 563 patients were randomized to the two trial arms with a 3:2 ratio in favour of CHART.

The standard radiotherapy regimen of 60 Gy in 30 fractions (2 Gy fractions) at 5 fractions per week is very similar to the UK standard (see 2.2). The intervention of interest (CHART) is both hyperfractionated (i.e. 1.5 Gy fractions) and accelerated (i.e. 3 fractions given per day for 12 days). The total radiation in the CHART arm (54 Gy) is less than the control arm (60Gy).

Patients were predominantly male (77%) 0.5% aged between 31-40 26% 71+, although the most patients (43%) were in the 61-70 age group. The majority of patients were stage IIIA/B (61%) and of squamous histology (82%), currently the most prevalent form of NSCLC in Europe. Patient characteristics were well balanced between the 2 trial arms. Patients were eligible for entry into the trial if they had inoperable NSCLC although 1 patient (0.5%) had SCLC.

This trial measured all 3 (i.e. survival, adverse events and quality of life data) outcomes considered important by this review although the quality of life data is reported separately[9]. The trial also measured clinical response and local and distant progression, disease free interval and performed a sub-group analysis particularly relating to tumour histology/type.

See Appendix 10 for tabulated characteristics of included studies

- **Included study quality**

Table 4 - Summary of trial quality using a modified Jadad score

	Ball 1999[3]	Bonner 1998 [4]	Kagami 1992[5]	Koca 1996[6]	Saunders 1999[2]	Sause-RTOG 2000[7]	Wang 1996[8]
Randomisation present	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Appropriate randomisation method	Yes	Yes	Yes	No	Yes	Can't tell	Can't tell
Concealment of allocation	Can't tell	Can't tell	Can't tell	Can't tell	Yes	Can't tell	Can't tell
Blinding of outcome assessors	Can't tell	Can't tell	Can't tell	Can't tell	No	Can't tell	Can't tell
Intention-to-treat analysis undertaken	Yes	Yes	Yes	No	Yes	Yes	Yes
Total Quality Score	**3/5**	**3/5**	**3/5**	**1/5**	**4/5**	**2/5**	**2/5**

For detailed description of quality criteria see appendix 4

(a) Quality of studies comparing accelerated regimens with standard radiotherapy

The one included trial[3] in this comparison was described as randomised and used an acceptable randomisation method. In the three trial arms of interest to this review (arms 1-3) there was a difference between arm 2 and the other 2 trial arms in terms of clinical stage, an important prognostic factor i.e. arm 2 had a higher % of patients with stage IIIA disease and a lower % of patients with stage IIIB disease. Since an adequate randomisation method was carried out this difference is likely to be due to the fact that trial arms were relatively small i.e. approximately 50 patients and even though before randomization patients were stratified according to prognostic factors of which there are several e.g. age, sex, stage and histology being the most important there were not enough patients to ensure an equal distribution of all prognostic factors in all trial arms. However no information was provided on concealment of allocation or blinding of assessors, which should have been possible. These factors were particularly badly reported in all trials in this review. An intention-to-treat analysis was performed for survival, however for adverse events 13 patients are missing although reasons are given.

(b) Quality of studies comparing hyperfractionated regimens with standard radiotherapy

There were three trials[5-7] included in this category. All three trials were described as randomised although the method was not described in any trial. No information was provided on concealment of allocation or on blinding of outcome assessors. In 2 of the trials[5,7] an intention-to-treat analysis was carried out, although in 1 trial[7] 32 patients were not included in this analysis as were deemed ineligible or were not properly entered. The exclusion of ineligible patients is not good practice and may therefore introduce bias.

(c) Quality of studies comparing hyperfractionated, split-course regimens with standard radiotherapy

There were two trials[4,8] in this category and both were described as randomised. In one of these trials[4] the randomisation procedure was described and considered to be appropriate. Again no information was provided on concealment of allocation or blinding of outcome assessors. In both trials it was considered that an intention-to-treat analysis was carried out.

(d) Quality of studies comparing combined accelerated/hyperfractionated regimens (e.g. CHART) with standard radiotherapy

Only 1 trial[2] was available for this comparison. It was described as randomized and the randomization procedure was adequate. Concealment of allocation was adequate but outcome assessors were not blinded. An intention-to-treat analysis was carried out.

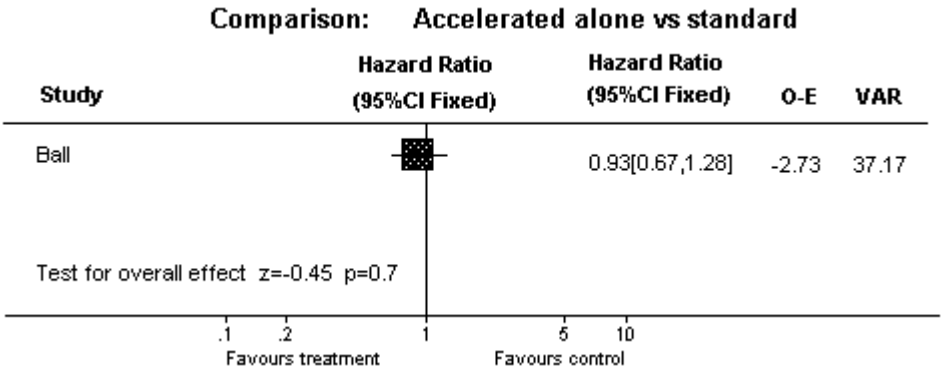
3.2.2 EFFECTIVENESS RESULTS

(a) Accelerated radiotherapy with or without adjuvant chemotherapy vs standard radiotherapy

- **Accelerated radiotherapy alone vs standard radiotherapy**

Primary outcome – survival

Only 1 trial[3] was identified for this comparison (99 patients), which reported a slight improvement in median survival for accelerated radiotherapy (median survival -13.8m-14.4m), however these results were not statistically significant and the analysis was only performed on stage III patients (78% of patients). The plot below for the hazard ratio illustrates the point that although the results tend to favour accelerated therapy over standard treatment, there is no clear evidence of benefit (see appendix 9 for methods).



Secondary outcomes

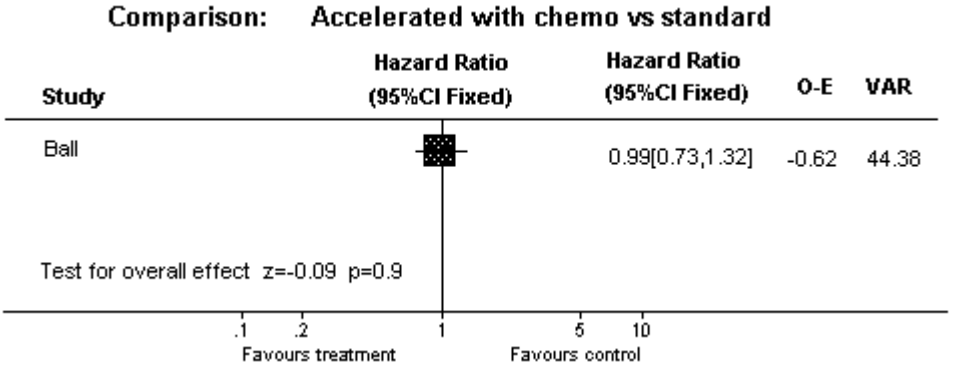
There was a significantly greater number and severity of oesophageal adverse events as expected in the accelerated trial arm due to the more aggressive nature of the therapy (15 acute grade 3/4 events vs 6 acute grade 3/4 events). There were no significant differences in clinical response between the trial arms (Response Rate i.e.Complete + Partial Responses : 53% vs 61%). Quality of life was not studied.

- **Accelerated radiotherapy with adjuvant chemotherapy vs standard radiotherapy**

Primary outcome – survival

Only 1 trial[3] available (104 patients) which reported a slight improvement in median survival for the accelerated trial arm (median survival 13.8m-15m), however the results were not statistically significant and the analysis was only performed on stage III patients (78% of patients).

The plot below for the hazard ratio shows that with a hazard ratio of 0.99, there is no clear evidence of benefit (see appendix 9 for methods).



Secondary outcomes

There was a significantly greater number and severity of oesophageal adverse events as expected in the accelerated trial arm due to the more aggressive nature of the therapy (24 grade 3/4 events vs 6 grade 3/4 events). Also overall the use of adjuvant chemotherapy in the trial resulted in significantly more grade 3/4 haematological adverse events (this is true of all trial arms using chemotherapy). There appeared to be fewer patients with a complete response (8% vs 17%) but more patients with partial response (51% vs 36%) in the accelerated arm although overall there were no real differences (Response Rate: 61% vs 53%) and none of significance. Again quality of life data was not studied.

Summary for trials on accelerated regimens

Overall it does not appear from this trial that accelerated regimens are associated with any improvement in clinical effectiveness, however they are associated with significantly more adverse events.

Although the trial was of moderate quality it was only a small trial and therefore it is difficult to base any solid conclusions on such data.

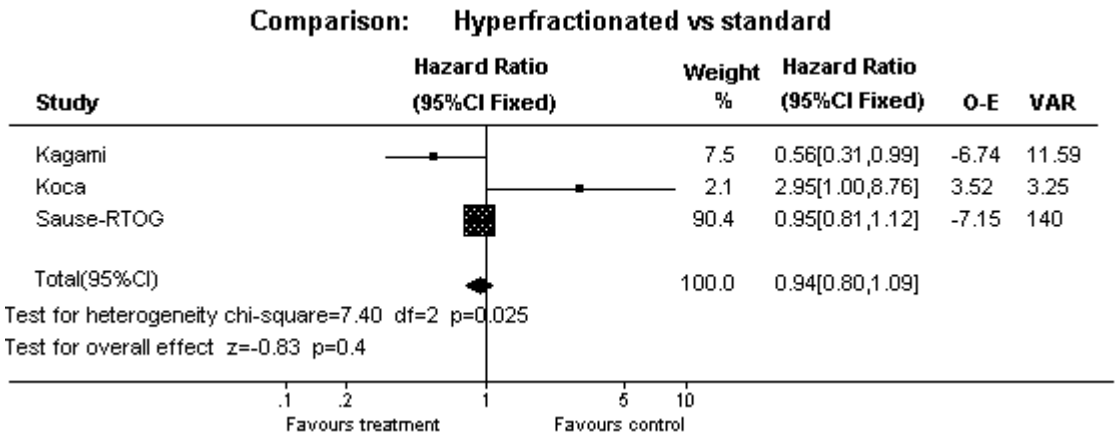
(b) Hyperfractionated radiotherapy with or without adjuvant chemotherapy vs standard radiotherapy

- **Hyperfractionated radiotherapy alone vs standard radiotherapy**

Primary outcome – survival

Three trials[5-7] with 361 patients in total, present data on this comparison. In the 2 trials[5,7] which measured % survival by year there appeared to be a small survival advantage in all years following treatment (see table 13-appendix 11) although none of these results were statistically significant. In the 2 trials[6,7] which reported median survival, one large trial (306 patients over all trial arms, including those relevant to this comparison) showed a small survival advantage for hyperfractionated therapy[7] (12m vs 11.4m) while the other trial[6] showed a small survival advantage for the standard treatment (14.5m (4-22) vs 9m (5-19)), however this trial had only 19 patients. Two of the trials[5,6] were small with only 36 patients each and one was fairly large with 490 patients over all trial arms, including those relevant to this comparison [7]. Neither demonstrated statistically significant differences in survival.

The hazard ratio plot below illustrates that combining the trials suggests that hyperfractionated therapy has a survival advantage over standard treatment although the confidence intervals cross the line of no difference. It should be noted that there is a lot of heterogeneity between the trials mainly due to the Koca trial[6] which is very small. There may also be problems stemming from the fact that the two smaller trials were not in English and therefore little information was available apart from that provided by translation. (see appendix 9 for methods).



Secondary outcomes

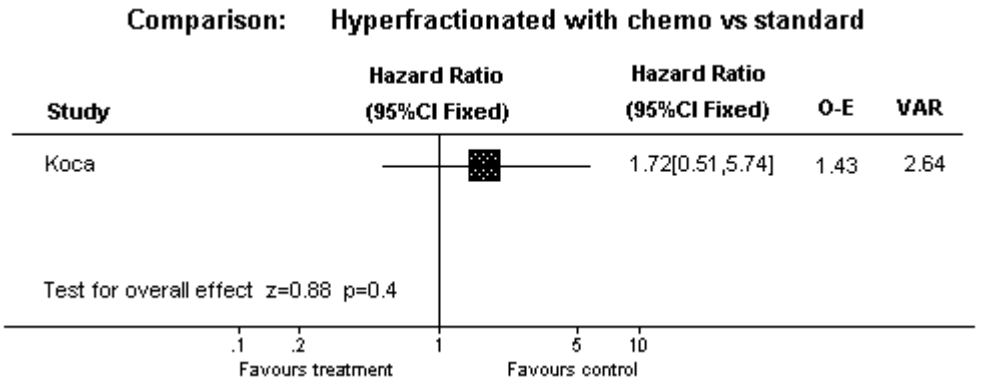
There were no significant differences in terms of any other outcome in any of the trial. Quality of Life was studied in a paper[26] containing some data from one of the included trials[7], however data was pooled from several trials including this trial and the estimate of survival was not consistent with that from the trial reported above, since data referring to this trial only could not be dissected out we did not consider it relevant to present this information.

- **Hyperfractionated regimens with adjuvant chemotherapy vs standard radiotherapy**

Primary outcome – survival

Only one small trial[6] was available for this comparison having only 17 patients providing data. Although the median survival for the hyperfractionated arm appears much shorter than that of the standard radiotherapy arm (14.5m vs 6m), the results are not statistically significant due to such small numbers of patients.

The plot below for the hazard ratio illustrates the point that although the results tend to favour the hyperfractionated therapy over standard treatment, the result is not significant due to such a small sample size because the apparent difference is consistent with chance (see appendix 9 for methods).



Secondary outcomes

The trial did not report any differences in any other outcome (quality of life not studied) although 3 patients overall (including those in the arm containing standard radiotherapy with chemotherapy) had chemotherapy discontinued due to adverse events.

Summary for trials on Hyperfractionated Radiotherapy

Overall there was so much heterogeneity in the outcomes of the included trials that is is difficult to draw any conclusion and therefore more evidence is needed. Importantly no trial reported any significant differences in terms of adverse events for the trials arms, however in the largest trial[7] there were 3 treatment related deaths associated with the hyperfractionation arm. In terms of hyperfractionated with adjuvant chemotherapy the one trial[6] available is so

small as to not provide any useful information in order to make any conclusions about effectiveness, again more research is needed in this area. It is worth noting that one of these trials[6] was considered to be of poor quality by this review, although this arose because important data in terms of quality was not reported.

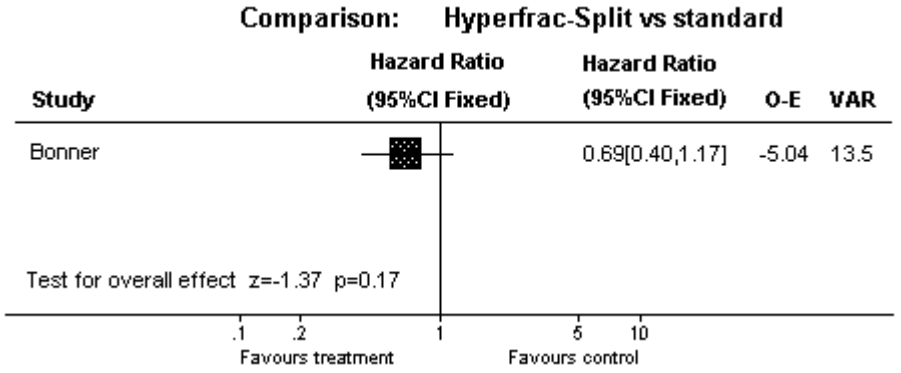
(c) Split-course hyperfractionated radiotherapy with or without adjuvant chemotherapy vs standard radiotherapy

- **Split-course hyperfractionated radiotherapy alone vs standard radiotherapy**

Primary outcome – survival

One[4] fairly small trial (67 patients in the comparable trial arms) was available to provide data on this comparison. Survival data was provided as survival curves and a p-value of 0.17 i.e. not statistically significant was given for the differences between the two trial arms.

The plot below for the hazard ratio suggests that the in terms of survival the treatment is favoured over the control (standard therapy) arm, although the result is not statistically significant (see appendix 9 for methods).



Secondary outcomes

There were no significant differences in any other outcome including adverse events, although one death was associated with standard radiotherapy. In terms of clinical response, there was an improvement in the hyperfractionated arm (Response Rate 45% vs 21%) and this result was statistically significance (p=0.04), although the usefulness of improvements in clinical response in determining clinical effectiveness is not known. Quality of life was not studied.

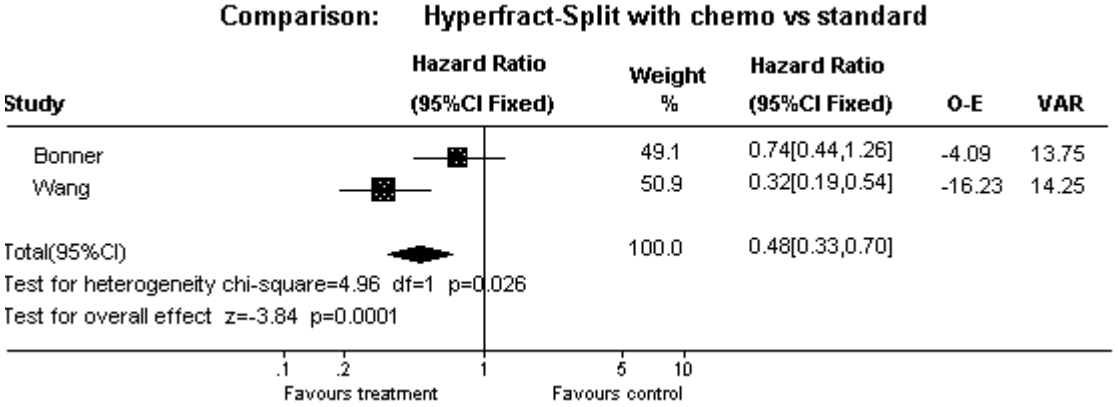
- **Split-course hyperfractionated radiotherapy with adjuvant chemotherapy vs standard radiotherapy**

Primary outcome - survival

Two trials[4,8] provided data for this comparison, again the trials were fairly small having 126 patients between them overall in the two trial arms being compared. One trial[4] provided no evidence of statistically significant differences between the two trial arms for survival

although there was a trend in favour of the split-course regimen, while the other trial[8] reported a statistically significant survival benefit in the hyperfractionated trial arm ($p<0.05$) for 1,2 and 3 year survival (1 year-80% vs 30%, 2-year-23% vs 7% and 3 year- 10% vs 0%). It is worth noting that this trial was considered to be of fairly poor quality due to lack of data.

The plot below suggests when the results are pooled the hyperfractionated arm of the trial is favoured over the control arm, although it is worth noting there is a high degree of heterogeneity between the trials (see appendix 9 for methods), although in this case the heterogeneity is due to disagreement as to the size, not the direction, of benefit.



Secondary outcomes

One trial[4] showed no statistically significant differences between any secondary outcome between trial arms. There appeared to be an improvement in clinical response in one trial[8] (Response Rate : 93% vs 64%) although it could not be determined from the paper if this was statistically significant. In this trial there did appear to be increased adverse events associated with the experimental arm although since only data on adverse events due to radiotherapy overall was provided it is impossible to make any formal comparison. Again quality of life was not reported.

Summary for trials on split-course, hyperfractionated radiotherapy

Overall there appears to be a possible survival advantage in the split-course hyperfractionated arms although again the chemotherapy may result in higher numbers of adverse events. Further research is required to provide a clearer answer.

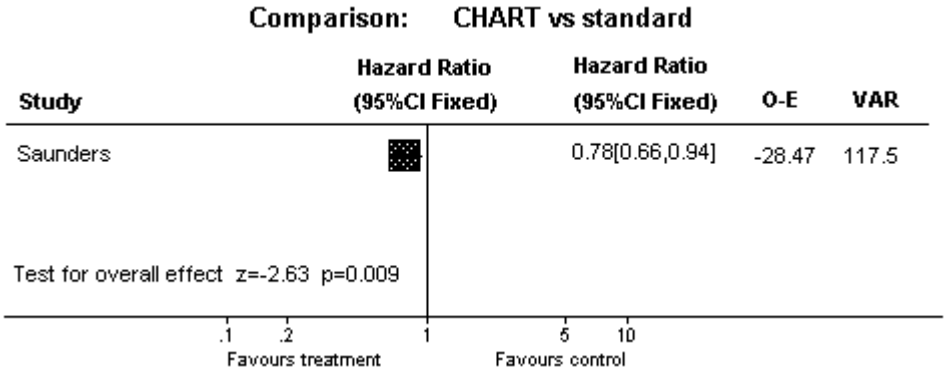
(d) Combined hyperfractionated/accelerated radiotherapy regimens with or without adjuvant chemotherapy vs standard radiotherapy

- CHART alone vs standard radiotherapy

Primary outcome – survival

One[2] large trial (562 patients) is available for this comparison and there appears to be a slight survival advantage in the CHART arm (median survival 13m vs 16.5m. Survival curves are given in the paper with corresponding log-rank p-values. The plot below of the hazard ratio supports the conclusion that the CHART trial arm has better survival potential than that of the

standard treatment (see appendix 9 for methods). A sub-group analysis in this trial showed a larger benefit with CHART for patients with squamous cell histology (7m vs 15m) although this result was not conclusive.



Secondary outcomes

There does appear to be a greater number of adverse events associated with the CHART arm although no p-values are provided for this (e.g. pulmonary fibrosis at 2 years in standard vs CHART arm (4% vs 16%), see also table 22-appendix 11.

A separate paper[25] provides information on quality of life data which was carried out on a subset of patients (approximately 64%) in this trial, however it was not possible to convert this data to a utility such as the QALY in order to use this in the cost-effectiveness calculations. There were very few differences between trial arms in terms of quality of life data, the only noted differences being significantly more cases of shortness of breath (p=0.03) and dizziness (p=0.03) in the exploratory data set on standard radiotherapy at 3 months following treatment and significantly more cases of pain on swallowing (p<0.002), pain (p=0.008) and heartburn (p=0.001) in the exploratory data set on the CHART arm at 21 days post-treatment. A confirmatory data set was used in order to confirm these findings and both pain on swallowing (p<0.001) and heartburn (p=0.02) were confirmed to be significantly greater on the CHART arm. There were no other significantly different results both short-term or long term using either the RSCL system[27] (Rotterdam System Checklist) or the HADS score[28] (Hospital Anxiety and Depression Scale).

- **CHART with adjuvant chemotherapy vs standard radiotherapy**

No trials were identified for this comparison

4. ECONOMIC ANALYSIS

The purpose of this section is to summarise and bring together information on the relative costs and net health benefits for each of the policy options for the management of NSCLC described in section 2.4. We were conscious that formal economic evaluations presenting either the cost/LYG or cost/QALY data for each of the policy options may well not be available in the literature. The search strategy was therefore broadened to allow identification of studies that may include information on resources or costs alone.

Data on health benefits in terms of overall survival are brought forward from the clinical effectiveness review to allow the cost effectiveness of the policy options to be presented as cost per life year gained (cost/LYG). Given the lack of quality of life data utility data it is not possible generate a cost per quality adjusted life year (QALY).

4.1 METHODS

4.1.1 Search strategy

A broad comprehensive search for studies assessing the clinical effectiveness and costs or quality of life of these 'non-conventional' radiotherapy regimens was undertaken involving:

- Electronic bibliographic database searches ; **MEDLINE** (Ovid) 1966-November 2001; **Embase** (Ovid) 1980-November 2001;**NHS EED** (NHS Economic Evaluation Database) 1966-November 2001 **Cochrane Library 2001** Issue 3 (see Appendix 2 for detail on search terms used)
- Citation checking of studies and reviews obtained
- Contact with experts in the field (see Appendix 3 for list)
- Internet search engines including lycos, excite and netscape.
- There were no language restrictions.

4.1.2 Inclusion/Exclusion Criteria

The inclusion and exclusion criteria were the same as those for effectiveness studies (see section 3.1.2). In addition studies were selected for inclusion if they included assessment of resource implications and or costs. A separate search for studies assessing quality of life was also undertaken. No language restriction was applied. Exclusion and inclusion criteria applied by one reviewer (RT) and checked by the other (BW).

4.1.3 Data extraction

Data concerning study characteristics, study quality and results was extracted by one reviewer (RT) and checked by the other (BW).

4.1.4 Quality Assessment Strategy

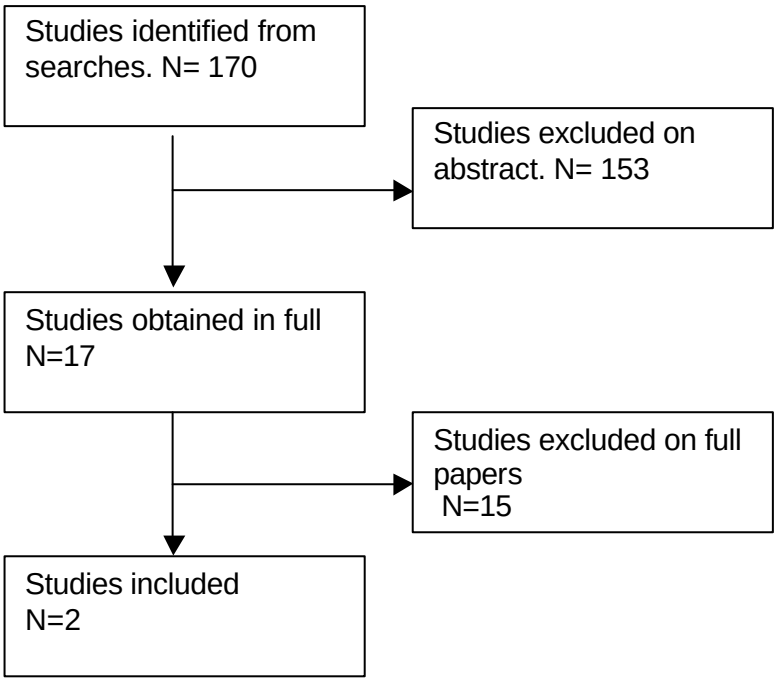
To assess the quality of included studies, in addition to their results, information on their study characteristics and methodological details were abstracted. The headings used were adapted from Drummond and Jefferson *'Guidelines for authors and peer reviewers of economic submissions to the BMJ'* checklist[29].

4.2 RESULTS

4.2.1 Quantity and quality of research available

- **Studies identified**

The search identified 170 studies of which 17 were obtained in full. From these only 2[10,11] were considered relevant and were included in the review (appendix 6)
Reasons for exclusion of studies are given in appendix 7 and include non-UK cost of illness studies, as healthcare provision for cancer management are known to have major differences to UK[30].



- **Characteristics of included studies**

Both included studies[10,11] are cost-impact studies. One[10] costs CHART vs standard radiotherapy in NSCLC in the UK, while the other[11] provides the costs of various management and treatment strategies for NSCLC in the UK. No cost-effectiveness studies were identified and no studies providing details of costs for hyperfractionated, split-course hyperfractionated or accelerated regimens were identified.

Table 5 - Characteristics and quality of included studies in economic analysis

	Coyle et al, 1997[10]	**Wolstenholme & Whymes, 1999**[11]
Country	UK	UK
Comparison	CHART versus conventional radiotherapy	Various management & treatment strategies
Population	NSCLC	NSCLC
Perspective	Societal & NHS costs	NHS costs only

Costs considered Radiotherapy treatment Outpatient visits GP consultations Bed days Other community services Patient travel	 √ √ √ √ √ √	 √ ? ? ? ? X
Source of medical costs	Clinical trial*	Trent hospitals audit (#227 patients)
Year of costs	1993-94	1993
Discount rate	None used	6%
Time horizon	3 months**	4 years*
Sensitivity analysis	No	No
Comments	*Detailed prospective identification of resources and costing undertaken **First 3 months of treatment	*4 years following diagnosis Details of included costs unclear

- **Results**

Costing data from the above studies was used to inform an analysis of cost effectiveness in terms of cost per life year gained.

Table 6 - Summary of health service costs, health benefits and cost effectiveness of policy options for management of NSCLC

Intervention being reviewed	Survival Difference in weeks with 95% CI*	Annualised costs of standard therapy with 95% CI*5	Annualised costs of intervention being reviewed*5	Cost Difference (means only)	Survival difference (years)	Cost per LYG and sensitivity analysis using 95% CI for survival difference
Accelerated radiotherapy alone	+3.74 (-35.8 to +24.8)	£6546.60 (5267.80 to £7825.40) *2	£6546.60 (5267.80 to £7825.40) *2	£0	0.072 (-0.69 to 0.48)	0
Accelerated radiotherapy with chemotherapy*4	+ 0.5 (-12.2 to +18.6)	£6546.60 (5267.80 to £7825.40) *2	£6682.60*2	+£136	0.0096 (-0.23 to 0.36)	£14,166 (dominant in favour of control to £378)
Hyperfractionated radiotherapy alone	+3.2 (-4.5 to +12.2)	£6546.60 (5267.80 to £7825.40) *2	Radiotherapy £4615.20 (range £3177.60-£6775.20) Other hospital £4222.32 (£3567.48-£4878.36) Overall £8837.52 Max £11653.66 Min £6745.08	+£2290.92	0.062 (-0.09 to 0.23)	£36,950 (dominant in favour of control to £9960)
Hyperfractionated radiotherapy with chemotherapy*4	-21.2 (-41.6 to +48.4)	£6546.60 (5267.80 to £7825.40) *2	Overall £8973.52 Max £11789.66 Min £6811.08	+£2426.96	-0.41 (-0.8 to 0.93)	Dominant in favour of control (dominant in favour of control to £2609)
Split-course hyperfractionated radiotherapy alone	+22.6 (-7.3 to +75.6)	£6546.60 (5267.80 to £7825.40) *2	Overall £8837.52 Max £11653.66 Min £6745.08	+£2290.92	0.45 (-0.14 to 1.45)	£5090 (dominant in favour of control to £1580)
Split-course hyperfractionated radiotherapy with chemotherapy*4	+54.6 (+21.6 to +102.3)	£6546.60 (5267.80 to £7825.40) *2	Overall £8973.52 Max £11789.66 Min £6811.08	+£2426.96	1.05 (0.42 to 1.97)	£2311 (£1231 to £5778)
CHART alone	+14.2 (+3.2 to +26)	£6546.60 (5267.80 to £7825.40) *2	£9577.80 (£9316 to £9838.84)*2	+£3031.20	0.27 (0.06 to 0.5)	£11227 (£6062 to £50,520)
CHART with chemotherapy	No studies available	No studies available	No studies available	No studies available	No studies available	No studies available

* See appendix 12 for method

*2 Costs for 3 months with standard deviations taken directly from Coyle and Drummond[10]. This data used to calculate annualised costs with 95% CI. In each case the 3 month cost corresponds to one radiotherapy regimen, therefore annualised costs would refer to four regimens.

*3 Costs for total hospital costs derived from figures given in Coyle and Drummond[10]. (see appendix 12)

*4 Costs for annual chemotherapy costs taken from Wolstenholme and Whymes[11] and taken to be £136.00 per year. (assumes all regimens would cost the same)

*5 Costs are hospital costs only and do not take into account community sector and societal and patient costs.

4.2.2 Assessment of cost-effectiveness

There was an absence of cost-effectiveness analysis studies for these regimens. The only cost data identified was a detailed cost study undertaken as part of the CHART trial[10]. From this data we estimated the costs of the other regimens with the limited information we were able to find including a paper on various management techniques of NSCLC[11]. The differences in costs between the non-conventional and standard regimens show that costs vary widely from £0 increase in costs to £3031 increase in costs per patients per year. In order to justify increased spending the non-conventional regimens should be more clinically effective, we have summarized this in terms of life years gained in the previous table. There were only two regimens (Split-course, hyperfractionated radiotherapy with chemotherapy (SC-HFX-RT+CT) and CHART) in which the cost per LYG was always positive (i.e. was not associated with a possible loss in survival-dominant in favour of the control). For SC-RT+CT the cost per LYG was £2311 (95% CI £1231 to £5778) and for CHART was £11,227 (95% CI £6062 to £50,520). Since costs and 95% CI for costs could be accurately determined from one of the included papers[31], we were able to also carry out a sensitivity analysis using minimum and maximum cost differences as well as differences in the survival estimate between CHART and the standard regimen. This resulted in a maximum cost per LYG of £76,183 and a minimum cost per LYG of £2980

We did not carry out this analysis on any other regimen because of the many assumptions made in order to determine their approximate costs and therefore we did not think it was appropriate to do so.

5. IMPLICATIONS FOR OTHER PARTIES

To determine if there will be any implications in terms of quality of life for patients and carers, additional data is necessary and should be a priority in any further trials. There do appear to be some negative quality of life effects much of which has been estimated from adverse events data in the included trials. The only regimen which appears to have significantly worse adverse events is that of accelerated radiotherapy. In the only trial where quality of life data was available[9] i.e. CHART there do appear to be some negative effects on quality of life with the new treatment, however there are also some improvements compared to the standard radiotherapy trial arm. These effects on patient quality of life appear to be short-term and long-term quality of life does not appear to differ between treatments. Intensive regimens such as CHART may be associated with inconveniences for patients and carers, however since there appear to be no differences in long term quality of life it is possible that patients will be willing to put up with short-term inconvenience in order to gain a potential survival advantage which will depend largely on the quality of that survival advantage for which more research is required. This conclusion however cannot be substantiated with trial evidence.

6. DISCUSSION

- **Main Results**

(a) Accelerated regimens

Only one relatively small trial was identified[3] in this area and that trial did not show any significant survival advantage over standard therapy with or without adjuvant chemotherapy (HR 0.99 (0.73 to 1.32) and 0.93 (0.57 to 1.28) respectively) Since the trial identified a significantly greater risk of severe adverse events and although there are no increased costs associated with this regimen (except £136 p.a. for chemotherapy), there is at present no evidence to suggest that this therapy should replace existing treatment. Since the trial is relatively small, further research is needed to prove this conclusion.

The trial was of moderate quality and therefore the reviewers have no reason to think that the results from this trial are not trustworthy.

(b) Hyperfractionated regimens

Three trials[5-7] were identified for this comparison although only one of these was of sufficient size[7]. Overall it would appear that there is a suggestion that hyperfractionated therapy alone may be associated with increased survival although not statistically significant (HR 0.94 (0.8 to 1.09)). When combined with adjuvant chemotherapy there appears to be a survival advantage in the control group (HR 1.72 (0.51 to 5.74)) although there were only 17 patients in the comparison and therefore the results are not statistically significant.

There were no significant differences in terms of adverse events between the regimens therefore this does not require consideration.

However there is an increased cost associated with hyperfractionated regimens of approximately £2300-£2400 per year, per patient and therefore further research is required in order to determine if there is in fact a significant survival advantage associated with these regimens.

The mean cost per LYG associated with these regimens is £36,950 (dominant in favour of control to £9960) for hyperfractionated therapy alone and dominant in favour of the control for the same regimen with chemotherapy. Again it should be noted that this data is based on one very small trial deemed to be of poor quality and therefore further evidence is vital to determine an accurate cost per LYG for hyperfractionated radiotherapy with chemotherapy.

If a sensitivity analysis is performed by removing the small trial responsible for the heterogeneity in the HFX v STD comparison i.e. Koca trial (also considered to be of poor quality due to lack of data provided), the mean cost per LYG is reduced to £23, 864 (i.e. combined HR of 0.91 (0.78 to 1.07))

(c) Split-course hyperfractionated regimens

Two trials were identified[4,8] for this comparison and with or without chemotherapy there was a suggestion of a survival advantage over standard therapy. Without chemotherapy this was not significant (HR 0.69 (0.4 to 1.17)) but for adjuvant chemotherapy the results are statistically significant (combined hazard ratio 0.48 (95% CI 0.33-0.7)).

However it cannot be determined whether this result is due to the radio therapy, chemotherapy or a combination of these factors since we have not compared this therapy to standard radiotherapy with chemotherapy.

There was a suggestion overall that the adjuvant chemotherapy arm may be associated with increased adverse events although not enough data was provided to determine this.

There is an estimated increase in costs associated with these regimens of approximately £2300 to £2400 per patient, per year.

The cost per LYG associated with these regimens is £5090 (dominant in favour of control to £1580) without chemotherapy and £2311 (£1231 to £5778) with chemotherapy.

It should be noted that one of the trials on which this data was based was considered to be of fairly poor quality[8] and the trials themselves were fairly small (126 relevant patients in total).

(d) Combined accelerated/hyperfractionated regimens (CHART)

One trial was available for this comparison [2], it was large (562 patients) and of good quality. There was a statistically significant survival advantage over standard treatment (hazard ratio 0.78 (95% CI 0.66-0.94)) and no significant differences in terms of adverse events.

The quality of life study determined the only differences between the treatments was significantly greater cases of pain on swallowing and heartburn (short-term effects) in the CHART arm. CHART is associated with an increase in costs of approximately £3000 per patient, per year.

The cost per LYG is £11,227 (£6062 to £50,520)

Since costs and 95% CI for costs could be accurately determined from one of the included papers[31], we were able to also carry out a sensitivity analysis using minimum and maximum cost differences as well as differences in the survival estimate between CHART and the standard regimen. This resulted in a maximum cost per LYG of £76,183 and a minimum cost per LYG of £2980

We did not carry out this analysis on any other regimen because of the many assumptions made in order to determine their approximate costs and therefore we did not think it was appropriate to do so.

It should be noted that this review did not include standard radiotherapy with chemotherapy as it was not determined to be an important policy question. However this review cannot therefore comment conclusively on whether regimens with chemotherapy are better because of the radiotherapy regimen or the chemotherapy since there is no control for this comparison.

- **Assumptions, limitations and uncertainties**

We believe that the search methods used were extensive and that his review is comprehensive in its coverage. Due to the small number of studies it was not reasonable to construct funnel plots to substantiate this.

It is clear that overall there was a lack of large RCTs considering that lung cancer is a highly prevalent disease in the Western World. The methods of reporting of the outcome we considered to be of primary importance i.e. overall survival was variable. We therefore had to use a variety of techniques in order to obtain approximate values for the hazard ratio and its variance in each of these trials (appendix 9).

Due to the lack of cost data we were only able to estimate cost differences (see table 25) for the various regimens and are therefore aware that this is a major limitation of the review. Another

limitation in all studies was the lack of quality of life data (although one trial did have a quality of life component it was not possible to convert this data into a QALY estimate) in terms of a QALY calculation which would have enabled the reviewers to provide a cost per QALY estimate for the interventions. Further trials should attempt to address this problem.

The comparability of regimens is also an issue where we had to make some assumptions i.e. that those regimens which we compared were indeed comparable e.g. hyperfractionated regimens when in fact they were slightly different. We also assumed that all standard regimens were comparable and although the majority were identical there were some notable differences (see table 3).

- **Implications for policy**

We have concluded in this review that 2 regimens (CHART and split-course, hyperfractionated radiotherapy with chemotherapy) are associated with a statistically significant survival advantage are also possibly cost-effective, and therefore this supports the implementation into clinical practice. However we do note that a major implication of this is the change in service which would need to take place in order to do this i.e. particularly those involving treatment out of hours. For this reason we believe that results from the CHARTW EL (CHART –weekend-less) trial[12] will provide very useful information which may mean changed in service may be easier to implement

- **Need for further research**

As already discussed the results from the CHARTWEL trial may prove particularly useful in the future but we feel it necessary to stress that a quality of life study making it possible to calculate QALYs and a well carried out cost-effectiveness study would be particularly useful in this area.

7. CONCLUSIONS

Quantity and quality of studies included

- 12 included studies on clinical-effectiveness were identified from searches providing data on 7 trials, 2 regimens (hyperfractionated radiotherapy alone and split-course, hyperfractionated radiotherapy with chemotherapy) had data provided by more than one trial.
- The standard/ conventional regimen was comparable between trials.
- Patients were predominantly male in all trials and varied in ages, the average age for most trials was between 60 and 70 years. All patients in all trials were relevant to this review.
- Trials took place over 4 continents (Asia, Europe, N. America and Australia) and ranged in size from 36 to 563 patients.
- Trials varied in quality from poor to good based on details provided in papers. No trial mentioned blinding of outcome assessors.
- No cost-effectiveness studies were available and two cost-impact studies were included in order to provide an estimate of associated differences in costs of non-conventional regimens compared to standard regimens.

Clinical-effectiveness

- Evidence from included trials suggested that there is a statistically significant survival advantage in two regimens (CHART and split-course, hyperfractionated radiotherapy with chemotherapy)
- These regimens were associated with relatively small increases in adverse events, although data from one trial on split-course, hyperfractionated radiotherapy with chemotherapy was unclear. Those which were statistically significant were short-term only (CHART).

Cost-effectiveness

- The cost per LYG was roughly estimated to be £11,227 (£6062 to £50,520) for CHART and £2311 (£1231 to £5778) for split-course, hyperfractionated radiotherapy with chemotherapy, although one of the trials on which this information is based was deemed to be of fairly poor quality while the CHART trial was considered to be of good quality. A sensitivity analysis on costs as well as effectiveness gave a cost per LYG for CHART with a maximum of £76,183 and a minimum of £2980. It was not considered appropriate to do this sensitivity analysis for any other regimen.

Implications

- Further QoL data is needed, particularly QALYs and/or cost-effectiveness studies.
- Further trials are needed in order to add to existing data, particularly for those regimens where trial data shows no statistically significant difference.
- The implications of implementing new regimens such as CHART for the NHS may be great, the biggest of which involves running the radiotherapy suite at weekends. For other regimens the implications may not be as great.
- Data from the CHARTWEL trial may provide useful data in the future.
- Implications for patients with these regimens may involve slightly higher cases of adverse events although these may be short-term and off-set by the survival advantage.

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Appendix 1 - Staging of non-small cell lung cancer

Staging of lung cancer is achieved using 3 parameters; tumour size (TX, T0, Tis, T1-4), regional lymph node status (NX, N0-3) and distant metastases (MX, M0 or M1) and is known as TNM classification.

The Revised International Staging System for Lung Cancer was adopted in 1997[32] by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer and the staging system which now reads:-

- Occult carcinoma : TX N0 M0
- Stage 0 : Tis N0 M0
- Stage IA : T1 N0 M0
- Stage IB : T2 N0 M0
- Stage IIA : T1 N1 M0
- Stage IIB : T2 N1 M0, T3 N0 M0
- Stage IIIA : T1 N2 M0, T2 N2 M0, T3 N1 M0, T3 N2 M0
- Stage IIIB : Any T N3 M0, T4, Any N M0
- Stage IV : Any T Any N M1

TNM classification[33]
Primary tumour (T)

TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0 Tis	No evidence of primary tumour Carcinoma-in-situ
T1	Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)
T2	Tumour with any of the following features of size or extent: more than 3 cm in greatest dimension; involving main bronchus, 2 cm or more distal to the carina; invading visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve entire lung
T3	A tumour of any size that directly invades any of the following: chest wall(including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium,; or tumour in the main bronchus les than 2cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
T4	A tumour of any size that invades any of the following: mediatinum, heart, great vessels, trachea, oesophagus, vertebral bosy, carina; or separate tumour nodules in the same lobe; or tumour with a malignant pleural effusion

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumour.
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis to contraleteral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Appendix 2 - Search Strategies

(a) The following search strategy was adapted from that designed to identify RCTs from the York CRD handbook and was aimed at detecting studies which could be considered to be randomized and contain a control group. For the intervention portion of the strategy fairly broad search terms were used in order to identify any relevant studies in the field. This search strategy was used to search Medline and Embase.

1. randomi#ed controlled trial.pt
2. randomi#ed controlled trials.sh
3. random allocation.sh
4. clinical trial.pt
5. exp clinical trials/
6. random.ti, ab
7. research design.sh
8. animal.sh
9. human.sh
10. 8 not (8 and 9)
11. 1 or 2 or 3 or 4 or 5 or 6 or 7
12. 11 not 10
13. exp lung neoplasms/
14. "continuous hyperfractionated accelerated radiotherapy".mp [mp=title, abstract, registry number word, mesh subject heading]
15. "continuous hyperfractionated accelerated radiation therapy".mp
16. "hyperfraction$".mp
17. "accelerat$".mp
18. "continuous".mp
19. 14 or 15 or 16 or 17 or 18
20. exp carcinoma, non-small-cell lung/
21. 13 or 20
22. 19 and 21
23. 12 and 22

(b) The following search strategy was used to identify relevant studies on clinical effectiveness in the CANCERLIT database since the above strategy could not be used.

1. "Non-small cell lung cancer" and
2. hyperfraction* and
3. radiotherapy
4. Filter for RCTs only selected
5. Filter for human studies only selected

(c) The following search strategy was used to identify studies of economic effectiveness and was used to search Medline and Embase. It was adapted from a York CRD (Centre for Reviews and Dissemination) report. The search was fairly broad to ensure that all studies including those purely on cost would be included and therefore we believe the search to be comprehensive.

1 Lung Neoplasms/
2 limit 1 to human
3 economics/
4 exp "costs and cost analysis"/
5 economic value of life/
6 cost of illness/
7 exp health care costs/
8 economic value of life/
9 exp economics medical/
10 exp economics hospital/
11 economics pharmaceutical/
12 exp "fees and charges"/
13 (cost or costs or costed or costly or costing).tw.
14 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
15 or/3-14
16 2 and 15

(d) The following search strategy was used to identify studies on the quality of life of patients with nsclc undergoing one of the treatments studied in this review:

1 Quality of Life/
2 Life Style/
3 Health Status/
4 Health Status Indicators/
5 Treatment Outcome/
6 "Outcome Assessment (Health Care)"/
7 1 or 2 or 3 or 4 or 5 or 6
8 exp lung neoplasms/
9 "continuous hyperfractionated accelerated radiotherapy".mp.
10 hyperfraction$.mp.
11 "accelerat$".mp. [mp=title, abstract, registry number word, mesh subject heading]
12 "continuous".mp. [mp=title, abstract, registry number word, mesh subject heading]
13 9 or 10 or 11 or 12
14 8 and 13
15 7 and 14
16 limit 15 to human
17 from 16 keep 1-108

Appendix 3 - Clinical Experts Contacted During Review

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Queen Elizabeth Hospital
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Appendix 4 - Details Of Quality Assessment

	Randomisation	Concealment of allocation	Blinding of assessors	ITT analysis
Ball 1999	Described as randomized and truly random Patients stratified acc. to prognostic factors and centrally randomised using adaptive biased coin procedure weighted to give balance between arms. Arm 2 has slightly higher % stage IIIA and less IIIB patients No other major differences noted in baseline prognostic factors	Unknown	Unknown	Yes (except for adverse events data-4 patients received little or no Rx and response –13 patients missing but reasons given)
Bonner 1998	Described as randomised and truly random as were centrally randomised following stratification by prognostic factors. There were no major differences between trial arms.	Unknown	Unknown	Yes, although not described as such it appears from the results to have taken place.
Kagami 1992	Described as randomised although the method is not described. There were no major differences noted in baseline prognostic factors between trial arms.	Unknown	Unknown	Yes – all patients received Rx to which they were allocated
Koca 1996	Described as randomized Block randomization used, patients stratified to 4 blocks by performance status and whether had lost <5% body weight over last 6m. Randomised was by admission order	Unknown	Unknown	No (86% protocol compliance - 2 excluded for protocol violation, 3 did not finish Rx, no losses to follow-up)
Saunders 1999	Described as randomized but procedure unknown except that there was a 2:1 randomisation in favour of CHART. No major differences noted in baseline prognostic factors between trial arms.	Yes	No	Yes
Sause-RTOG 2000	Not described as randomized and if we assume it to have taken place the procedure is unknown. No major differences noted in baseline prognostic factors between trial arms	Unknown	Unknown	Yes – 28 deemed ineligible and 4 not properly entered (Unlikely to be a source of bias) 5 losses to follow-up in arm 3
Wang 1996	Not described as randomized although it did take place but procedure is unknown. Arm 1 has a higher % of patients <60 yrs compared to arm 4 i.e. 55% and 37% respectively. No other major differences noted in baseline prognostic factors	Unknown	Unknown	Yes

Appendix 5 - Included Studies On Clinical Effectiveness

(1) Bailey AJ, Parmar MK, Stephens RJ. Patient-reported short-term and long-term physical and psychologic symptoms: results of the continuous hyperfractionated accelerated [correction of acclerated] radiotherapy (CHART) randomized trial in non-small-cell lung cancer. CHART Steering Committee. Journal of Clinical Oncology 1998; 16(9):3082-3093.

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(12) Wang G, Song M, Xu H, Fang Y. Prospective trial of combined hyperfractionated radiotherapy and bronchial arterial infusion of chemotherapy for locally advanced nonsmall cell lung cancer. International Journal of Radiation Oncology, Biology, Physics 1996; 34(2):309-313.

Appendix 6 - Included Studies On Cost-Effectiveness

(1) Coyle D, Drummond MF. Costs of conventional radical radiotherapy versus continuous hyperfractionated accelerated radiotherapy (CHART) in the treatment of patients with head and neck cancer or carcinoma of the bronchus. Clinical Oncology 1997; 9:313-321.

Appendix 7 - Excluded Studies On Cost-Effectiveness

This appendix reports the studies obtained in full from the searches which were excluded from the review due to not being relevant.

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Appendix 8 - Data Extraction Forms

(a) STUDY CHARACTERISTICS		Study ID Number	Study ID Number
Country of trial and dates entered			
Interventions	ARM 1		
	ARM 2		
	ARM 3		
	ARM 4		
Type of radiotherapy regimen			
Chemotherapy			
Number randomised	ARM 1		
	ARM 2		
	ARM 3		
	ARM 4		
Demographics (all)	Age -median+range		
	Sex		
	Stage		
	Histology		
Age- median+range	ARM 1		
	ARM 2		
	ARM 3		
	ARM 4		
Sex - % male	ARM 1		
	ARM 2		
	ARM 3		
	ARM 4		
Clinical Stages	ARM 1		
	ARM 2		
	ARM 3		
	ARM 4		
Histology	ARM 1		
	ARM 2		
	ARM 3		
	ARM 4		
Eligibility: Age Stage Performance status Previous treatment Weight loss			
Exclusion Criteria; excluded if:			
Pre-treatment tests carried out			
Outcomes in trial			
Response Criteria Definitions Complete Response (CR) Partial Response (PR) Stable Disease (SD) Progressive Disease (PD)			

(b) RESULTS	Study ID Number :			
(i) SURVIVAL	**ARM 1**	**ARM 2**	**ARM 3**	**ARM 4**
1 year survival				
2 year survival				
3 year survival				
4 year survival				
5 year survival				
Median survival and range				
Hazard ratio and variance				
p-values				
(ii) ADVERSE EVENTS				
Acute Grade 3				
CAcute Grade 4				
Late Grade 3				
Late Grade 4				
Deaths due to intervention				
p-values				
(iii) QUALITY OF LIFE DATA				
(iv) CLINICAL RESPONSE				
Complete Response				
Partial Response				
Response Rate (CR + PR)				
Stable Disease				
Progression				
p-values				

(c) STUDY QUALITY	Study ID Number:
Is trial described as randomised? Is the trial truly random i.e. are details of the randomisation procedure given?	
Is there evidence of concealment of allocation?	
Were outcome assessors blinded?	
What was the loss to follow-up? Was an intention-to-treat analysis performed?	
Are there any missing data?	
Any major differences in prognostic factors between trial arms?	

Appendix 9 - Methods Of Meta-Analysis

Survival data extraction

The appropriate summary statistic for use with survival (time to event) data is the hazard ratio, which summarises the difference between two Kaplan-Meier survival curves and represents the overall relative risk of death over the period of follow-up of patients. This is preferable to simple comparisons of the overall number of events or the odds of survival at fixed timepoints [20]

In order to combine survival data from different trials, an estimate of the log hazard ratio and it's variance for each trial is needed.

The pooled hazard ratio (HR) and associated 95% confidence interval are calculated (using the fixed effects model) as follows:

$$\ln(HR) = \frac{\sum\left(\frac{\ln(HR_i)}{Var[\ln(HR_i)]}\right)}{\sum\left(\frac{1}{Var[\ln(HR_i)]}\right)}$$

$$Var[\ln(HR)] = \frac{1}{\sum\left(\frac{1}{Var[\ln(HR_i)]}\right)}$$

The pooled hazard ratio and associated 95% confidence interval are given by:-

$$\exp\left\{\ln(HR) \pm 1.96\sqrt{Var[\ln(HR)]}\right\}$$

Information available from trial reports

The log hazard ratio and it's variance are rarely reported directly, but methods are available to estimate these from other summary statistics or from the published Kaplan-Meier survival curves[20]. The methods used to obtain estimates for each trial were, briefly, as follows:

Ball

The proportions surviving at annual intervals up to 6 years from randomisation were read from the published Kaplan-Meier survival curves. The trial report gives the numbers at risk at one year intervals. The log hazard ratio and it's variance were estimated from these data using the methods described by *Parmar et al*[20].

Kagami

The proportions surviving at 10 month intervals up to 40 months from randomisation were read from the published Kaplan-Meier survival curves. A 10 month interval was used because the time

axis on the published curves was marked at 10 month intervals. The paper is published in Japanese and censored survival times are not marked on the Kaplan-Meier curves, so it was not possible to obtain estimates of minimum and maximum follow-up from the paper. Values of 1 month and 50 months were used. The log hazard ratio and it's variance were estimated from these data using the methods described by *Parmar et al.*[20] It should be noted that the sample size for this trial is very small and this approach may therefore not be particularly reliable; we have no alternative method available due to the very limited information available from this trial. In particular, the value for the variance obtained appears to be a substantial under-estimate and so this trial may have a greater influence on the pooled results than merited by it's relative sample size.

Koca

This small trial reports the survival times (in months) of all patients. The log hazard ratio and it's variance were calculated from this data using the Mantel-Haenszel method [41]

Sause

The proportions surviving at annual intervals up to 6 years from randomisation were read from the published Kaplan-Meier survival curves. Minimum and maximum follow-up were estimated from the Kaplan-Meier survival curves (which indicated censored survival times). The log hazard ratio and it's variance were estimated from these data using methods described by *Parmar et al.*[20]

Bonner

This trial report gives very limited information. The number of patients dying on each arm is not given, but the total number of deaths (in all three arms) was reported. The number dying on each arm was estimated from the reported proportions surviving at the end of the trial. An approximate value of the variance of the log hazard ratio was obtained for each comparison using the estimated number of deaths. An approximate value for the hazard ratio was then obtained using the reported logrank p-value for each comparison, using the methods described by Parmar *et al.*[20]

Wang

The number of patients surviving at 1, 2 and 3 years are reported. This information was used to obtain estimates of the log hazard ratio and it's variance for the first, second and third years. These estimates were combined to provide overall estimates.

Saunders

This trial reports the hazard ratio with a 95% confidence interval. However after contact with the trialists we were supplied with the values of O-E and v, the hazard ratios and confidence intervals supplied directly were not different from the published data and should therefore not introduce any bias.

Appendix 10 - Characteristics Of Included Studies

Table 7 - Characteristics of studies comparing accelerated regimens to standard radiotherapy

	Ball 1999[3]			
(A) Study characteristics				
Number randomized	**208** (204 assessed-4 discovered ineligible after randomization)			
Country of trial	Australia			
Dates entered	01/04/89 -16/05/95			
Trial type (as described in paper)	Multicentre randomized phase III study			
Interventions ARM 1	**STD-RT** : 60 Gy in 30 fractions, 5 per week for 6 weeks			
ARM 2	**ACC-RT** : 60 Gy in 30 fractions, 10 per week for 3 weeks			
ARM 3	**STD-RT + CT** - iv carboplatin 70mg/m^2/ day days 1 to 5 and days 29 to 33 of RT			
ARM 4	**ACC-RT + CT** - iv carboplatin 70mg/m^2/ day on days 1 to 5			
Chemotherapy	Carboplatin			
(B) Patient Characteristics				
Demographics (overall)				
Age -median+range	Not given			
Sex	77% male			
Stage	18% I, 3% II, 50% IIIA, 29% IIIB			
Histology	64% squamous, 36% non-squamous			
Demographics by trial arm	**ARM 1**	**ARM 2**	**ARM 3**	**ARM 4**
Number (%)	**53** (26%)	**46** (23%)	**54** (26%)	**51** (25%)
Age- median+range	62 (42-77)	65 (40-78)	68 (47-79)	66 (46-77)
Sex - % male	79%	74%	81%	75%
Clinical Stages	19%I, 2%II, 44%IIIA, 36%IIIB	20%I, 2%II, 61%IIIA, 17%IIIB	15%I, 9%II, 46%IIIA, 30%IIIB	18%I, 2%II, 49%IIIA, 31%IIIB
Histology	64% squamous, 36% non-squamous	63% squamous, 37% non-squamous	67% squamous, 33% non-squamous	61% squamous, 39% non-squamous
(C) Inclusion/Exclusion Criteria				
Eligible if:	Any stage if disease inoperable, ECOG performance status 0 or 1, No previous treatment, Weight loss <10%			
Exclusion Criteria; excluded if:	Granulocyte count <1.5x10^9/l, platelet count<100x10^9/l, cancer outside of primary site and regional nodes.			
Pre-treatment tests:	Medical History, Physical examination, Blood Tests/Biochemistry, Radiographs, CT scans, Pulmonary Function Tests.			
(D) Outcomes				
Outcomes studied in trial	Overall survival, Local and distant progression, Adverse events, Clinical response			
Response Criteria Definitions Complete Response (CR) Partial Response (PR) Stable Disease (SD) Progressive Disease (PD)	 Disappearance of all disease lasting at least 4 weeks. Reduction of at least 50% in tumour size for at least 4 weeks. No change or <50% reduction or < 25% increase in tumour size Increase of 25% or more in tumour size			

Notes : STD-RT: Standard/conventional radiotherapy regimen CT: Chemotherapy ACC-RT: Accelerated radiotherapy RCT: Randomised controlled trial
ECOG : Eastern Co-operative Oncology Group

Table 8 - Characteristics of studies comparing hyperfractionated regimens to standard radiotherapy

	Kagami 1992[5]	Koca 1996[6]	Sause-RTOG 2000[7]
(A) Study characteristics			
Number randomized	36	36	490 (458 assessed)
Country of trial	Japan	Turkey	USA/Canada
Dates entered	09/87 – 08/90		20/01/89-25/01/92
Trial type (described)	Prospective randomized trial	Phase III randomized clinical trial	Phase III clinical trial (multicentre)
Interventions ARM 1	**STD-RT**	**STD-RT**	**STD-RT**
ARM 2	**HFX-RT**	**HFX-RT**	**STD-RT + CT**
ARM 3	n/a	**STD-RT + CT** :	**HFX-RT**
ARM 4	n/a	**HFX-RT + CT:** cisplatin 20mg, fluorouracil 300mg, VP-16 50mg dys 1-5 and repeated at 4th week of RT. After RT-cisplatin 25mg, etopside 120mg, ifospamide 2g, uromitexan 3x400mg dy 1-3, all at 6x at 4 wk intervals)	n/a
(B) Patient characteristics			
Demographics (all) Age -median+range Sex Stage Histology	Not given 97% male 69% IIIA, 21% IIIB 69% squamous, 22% adenocarcinoma, 9% large cell	57 (33-67) 88% male Not given 75% squamous, 11% adenocarcinoma, 11% unknown	38%<60 , 62% >60 70% male 6%II,45%IIIA,49%IIB 44% squamous, 34% adenocarcinoma, 11% large cell, 11% other
Age- median+range ARM 1 ARM 2 ARM 3 ARM 4	65 (42-76) 65 (51-75) n/a n/a	Not given	Not given Not given Not given n/a
Sex - % male ARM 1 ARM 2 ARM 3 **ARM 4**	94% 100% n/a n/a	Not given	68% 72% 71% n/a
Clinical Stages ARM 1 ARM 2 ARM 3 ARM 4	61% IIIA, 39% IIIB 78% IIIA, 22% IIIB n/a n/a	Not given	6% II, 44% IIIA, 50% IIIB 6% II, 45% IIIA, 48% IIIB 4% II, 46% IIIA, 50% IIIB n/a
Histology ARM 1 ARM 2 ARM	61% squamous, 33% adenocarcinoma, 6% large cell 83% squamous, 11% adenocarcinoma, 6% large cell n/a	Not given	45% squamous, 8% large cell, 33% adenocarcinoma, 14% other 43% squamous, 11% large cell, 38% adenocarcinoma, 8% other 44% squamous, 14% large cell, 31% adenocarcinoma, 11% other

(C) Inclusion/Exclusion criteria			
Eligible if:	Stage III patients with 'good' performance status	< 70 yrs, Stage II or III nsclc, WHO PS 0-2, No previous Rx	≥ 18 yrs, II/IIIA/IIIB NSCLC, KPS ≥ 70% No previous Rx, weight loss < 5% 3 m before study entry
Exclusion Criteria; excluded if:	Not given	Did not have sufficient haematopoetic, renal and liver function. If had other serious illness such as diabetes, TB or mental disorders.	Any metastatic disease, pleural effusion.
Pre-treatment tests:	Not given	Blood tests/Biochemistry, Radiographs, CT scans	Medical History, Physical examination, Blood Tests/Biochemistry, Radiographs, CT scans, Pulmonary Function Tests.
(D) Outcomes			
Outcomes studied in trial	Overall survival Adverse events Clinical Response	Overall survival Adverse events Clinical Response	Overall Survival Survival sub-group analysis performed (age and cancer type) Adverse events
Response Definitions	None given	None given	n/a

Notes : STD-RT: Standard/conventional radiotherapy regimen CT: Chemotherapy VP-16: Epipodophyllotoxin etopside
HFX-RT: Hyperfractionated radiotherapy regimen KPS: Karnofsky performance status WHO PS: World Health Organisation performance status

Table 9 - Characteristics of studies comparing hyperfractionated, split-course regimens to standard radiotherapy

	Bonner 1998[4]	Wang 1996[8]
(A) Study characteristics		
Number randomized	110 (99 assessed)	126
Country of trial	USA	China
Dates entered	04/92 – 10/93	01/88-01/90
Trial type (described)	Phase III randomized trial	Prospective trial
Interventions ARM 1	**STD-RT**	**STD-RT**
ARM 2	**HFX-RT**	**STD-RT + CT**
ARM 3	**SCHFX -RT + CT** : cisplatin (30mg/m², days 1-3 and 28-30) and etopside 100mg/m² days 1-3 and 28-30)	**SC-RT + CT**
ARM 4	n/a	**SCHFX -RT + CT** **CT :** DDP 60mg, Adramycin 40mg,for ac only+ mitomycin 10mg or VP-16 100mg
(B) Patient characteristics		
Demographics (all) Age -median+range Sex Stage Histology	 64 (42-86) 63% male 60% IIIA, 40% IIIB 40% squamous, 60% non-squamous	 54%<60, 46%%=60 90% male 32% II, 68% III 63% squamous, 23% adenocarcinoma, 14% large cell

Age- median+range		
ARM 1	65 (42-86)	55%<60 , 45%>60
ARM 2	64 (47-81)	61%<60 , 39%>60
ARM 3	62 (46-82)	67%<60 , 33%>60
ARM 4	n/a	37%<60 , 63%>60
Sex - % male		
ARM 1	65% male	97%
ARM 2	64% male	88%
ARM 3	59% male	82%
ARM 4	n/a	93%
Clinical Stages		
ARM 1	65% IIIA, 35% IIIB	27% II, 73% III
ARM 2	61% IIIA, 39% IIIB	39% II, 61% III
ARM 3	53% IIIA, 57% IIIB	30% II, 70% III
ARM 4	n/a	30% II, 70% III
Histology		
ARM 1	38% squamous, 62% non-squamous	70% squamous, 20% adenocarcinoma, 10% large cell
ARM 2	42% squamous, 58% non-squamous	64% squamous, 21% adenocarcinoma, 15% large cell
ARM 3	41% squamous, 59% non-squamous	55% squamous, 27% adenocarcinoma, 18% large cell
ARM 4	n/a	67% squamous, 23% adenocarcinoma, 10% large cell
(C) Inclusion/Exclusion criteria		
Eligible if:	Stage III , weight loss <10%, ECOG PS 0-2, serum chemistries within acceptable limits, FEV_1 1L or more or at least 40% of predicted value.	> 18 yrs, Any stage if inoperable NSCLC, ECOG PS 0-2 only
Exclusion Criteria; excluded if:	MI within 3 months, CHF, arrhythmia, prev CT for CA or prev RT for lung CA, major surgery < 2 weeks previously, previous CA <3 years since diagnosis of lung CA (xcpt skin or in-situ cervical)	Other CA (xcpt nonmelanomatous skin CA, cervical or breast CA in-situ), other symptomatic pulmonary or CVS dx, if did not have adequate haematologic, renal and hepatic function and if FEV_1<1
Pre-treatment tests:	Medical History, Physical examination, Blood Tests/Biochemistry, Radiographs, CT scans, Pulmonary Function Tests, ECG.	Medical History, Physical examination, Blood Tests/Biochemistry, Radiographs, CT scans, Pulmonary Function Tests.
(D) Outcomes		
Outcomes studied in trial	Overall survival Progression-free survival Adverse events Clinical Response	Overall survival Adverse events Clinical Response
Response Definitions		
Complete Response	Disappearance of all tumour	Disappearance of all tumour
Partial Response	=50% ? tumour size	50% decrease in tumour size
Stable Disease	<50% ? or <25% ? tumour size	SD and PD not defined but No response defined as no change in tumour size or <
Progressive Disease	=25% ? in size or appearance of new lesion	50%? in size

Notes : STD-RT: Standard/conventional radiotherapy regimen CT: Chemotherapy VP-16: Epipodophyllotoxin etopside CP: Cyclophosphamide
HFX-RT: Hyperfractionated radiotherapy regimen CA : Cancer SCRT: Split -course radiotherapy regimen
ECOG: Eastern Co -operative Oncology Group

Table 10 - Characteristics of studies comparing combined Hyperfractionated/accelerated regimens (CHART) with standard radiotherapy

	Saunders 1999[2]	
(A) Study characteristics		
Number randomized	**563**	
Country of trial	UK/Europe	
Dates entered	01/04/90 -31/03/95	
Trial type (as described in paper)	Multicentre randomized trial	
Interventions ARM 1	**STD-RT**	
ARM 2	**CHART**	
Chemotherapy	None	
(B) Patient Characteristics		
Demographics (overall) Age -median+range Sex Stage Histology	 Not given 77% male 6% IA, 23% IB, 7% II, 38% IIIA, 23% IIIB, 3% unknown Not given	
Demographics by trial arm	**ARM 1**	**ARM 2**
Number (%)	225 (40%)	338 (60%)
Age- median+range	31% < 60, 69% > 60yrs	31% < 60, 69% > 60yrs
Sex - % male	74%	79%
Clinical Stages	5% IA, 25% IB, 7% II, 38% IIIA ,23% IIIB ,2%unknown	7% IA, 22% IB, 7% II, 38% IIIA, 23% IIIB, 3%unknown
Histology	84%squamous,6%large cell,6%adenocarcinoma,2%nsclc unknown,1%carcinoma-in-situ	81%squamous,6%large cell,7%adenocarcinoma,6%nsclc unknown,1%small cell lung cancer
(C) Inclusion/Exclusion Criteria		
Eligible if:	Inoperable nsclc, WHO PS 0-2, No previous treatment	
Exclusion Criteria; excluded if:	None stated	
Pre-treatment tests:	Not stated although assumed to have taken place as tests (CT scans, x-rays) performed as assessments following treatment.	
(D) Outcomes		
Outcomes studied in trial	Overall Survival, Survival by sub-group analysis, Adverse events, Quality of Life data (reported elsewhere), local tumour control, disease free interval, metastasis free interval.	
Response Criteria Definitions Complete Response (CR) Partial Response (PR) Stable Disease (SD) Progressive Disease (PD)	Clinical response not studied but local tumour control defined as either complete disappearance of all abnormalities in x-ray or CT scan, or when any residual abnormality seen at 6m remains stable for a further 6m.	

Notes : STD-RT: Standard/conventional radiotherapy regimen CHART: Continuous Hyperfractionated Accelerated Radiotherapy
WHO PS: World Health Organisation performance status

Appendix 11 - Results Of Clinical Effectiveness From Included Studies

Table 11 - Accelerated regimens compared to standard radiotherapy – survival

	Ball 1999[3]	
	ARM 1	**ARM 2**
Number of patients	53	46
Intervention	STD-RT	ACC-RT
Hazard ratios and CI	Not given	
% survival by year 1 year (95% CI) 2 year (95% CI) 3 year (95% CI)	 60 (45-74) 26 (13-40) 10 (1-18)	 61 (45-77) 28 (13-42) 13 (1-24)
Median survival (months)	13.8 (stage III only 78% of all patients)	14.4 (stage III only 78% of all patients)
p-values	None given but described as non-significant	

Table 12 - Accelerated regimens compared to standard radiotherapy – secondary outcomes

	Ball 1999[3]	
	ARM 1	**ARM 2**
Number of patients	53	46
Intervention	STD-RT	ACC-RT
Adverse effects		
Acute grade 3	1 haematological event, oesophageal events in 4 patients.	No haematological events, oesophageal events in 13 patients.
Acute grade 4	No haematological events, oesophageal events in 2 patients.	No haematological events, oesophageal events in 2 patients.
Late grade 3	Not stated	Not stated
Late grade 4	Not stated	Not stated
Treatment related deaths	None	3
Statistically significant differences	Severity and median duration of oesophagitis was significantly greater/longer in patients receiving ACC-RT.	
Quality of Life data – Not studied		
Clinical Response		
Complete Partial Stable Disease Progressive Disease Response Rate (CR + PR) Missing	17% 36% 28% 11% 53% 8%	15% 46% 24% 11% 61% 4%
p-values	None but described as non-significant	

Table 13 - Accelerated regimens with adjuvant chemotherapy compared to standard radiotherapy - survival

	Ball 1999[3]	
	ARM 1	**ARM 4**
No. of patients	53	51
Intervention	STD-RT	ACC-RT + CT (carboplatin)
Hazard ratios and CI	Not given	
% survival by year 1 year (95% CI) 2 year (95% CI) 3 year (95% CI)	 60 (45-74) 26 (13-40) 10 (1-18)	 59 (43-74) 20 (7-32) 5 (0-13)
Median survival (months)	13.8 (stage III only 78% of all patients)	15 (stage III only 78% of all patients)
p-values	None given but described as non-significant	

Table 14 - Accelerated regimens with adjuvant chemotherapy compared to standard radiotherapy – secondary outcomes

	Ball 1999[3]	
	ARM 1	**ARM 4**
No. of patients	53	51
Intervention	STD-RT	ACC-RT + CT (carboplatin)
Adverse effects		
Acute grade 3	1 haematological event, oesophageal events in 4 patients.	3 haematological events, oesophageal events in 23 patients.
Acute grade 4	No haematological events, oesophageal events in 2 patients.	No haematological events, oesophageal events in 1 patient.
Late grade 3	Not stated	Not stated
Late grade 4	Not stated	Not stated
Rx related deaths	None	2
p-values	Not given but severity and median duration of oesophagitis was significantly greater/longer in patients receiving ACC-RT (overall) and significantly more grade 3/4 haematological events in patients treated with carboplatin (overall).	
Quality of Life data – Not studied		
Other – Clinical Response		
Complete Partial Stable Disease Progressive Disease Response Rate (CR + PR) Missing	17% 36% 28% 11% 53% 8%	8% 51% 29% 4% 61% 8%
p-values	None given but described as non-significant	

Table 15 - Hyperfractionated regimens compared to standard radiotherapy - survival

	Kagami 1992[5]		Koca 1996[6]		Sause-RTOG 2000[7]	
	ARM 1	**ARM 2**	**ARM 1**	**ARM 2**	**ARM 1**	**ARM 3**
No. of patients	18	18	10	9	152	154
Intervention	STD-RT	HFX-RT	STD-RT	HFX-RT	STD-RT	HFX-RT
Hazard ratios	Not given		Not given		Not given	
% survival by year 1 year (95% CI) 2 year (95% CI) 3 year (95% CI) 4 year (95% CI) 5 year (95% CI)	 61.1% 31.3% 0% Not given Not given	 66.7% 50% 21.8% Not given Not given	Not given		 47% 21% 11% 6% 5%	 52% 24% 14% 9% 6%
Median survival (months)	None given	None given	14.5 (4-22)	9 (5-19)	11.4	12
p-values	None given but described as non-significant		None given but described as non-significant		None given but described as non-significant	

Table 16 - Hyperfractionated regimens compared to standard radiotherapy – secondary outcomes

	Kagami 1992[5]		Koca 1996[6]		Sause-RTOG 2000[7]	
	ARM 1	**ARM 2**	**ARM 1**	**ARM 2**	**ARM 1**	**ARM 3**
No. of patients	18	18	10	9	152	154
Intervention	STD-RT	HFX-RT	STD-RT	HFX-RT	STD-RT	HFX-RT
Adverse effects						
Acute grade 3	7 patients (38.9%) had fever	4 patients (22.2%) had fever	None	None	Acute > grade 3, 1 in arm 1 and 4 in arm 3	
Acute grade 4			None	None		
Late grade 3			None	None	Late > grade 3, 3 in arm 1 and 5 in arm 3	
Late grade 4			None	None		
Rx related deaths	None	None	None	None	0	3+
p-values	None given		None given but described as non-significant		None given but described as non-significant	
Quality of Life data – Not studied						
Other-Clinical Response						
Complete Partial Stable dx Progressive dx Response Rate (CR + PR) Missing Regression	16.7%	44.4%	Reported as tumour response > 50% in 20 patients and < 50 % in 10 patients. No other information given.		Not studied	
p-values	None given		None given but described as non-significant		n/a	

Table 17 - Hyperfractionated regimens with adjuvant chemotherapy compared to standard radiotherapy - survival

	Koca 1996[6]	
	ARM 1	**ARM 4**
No. of patients	10	7
Intervention	STD-RT	HFX-RT + CT
Hazard ratios	Not given	
% survival by year 1 year (95% CI) 2 year (95% CI) 3 year (95% CI) 4 year (95% CI) 5 year (95% CI)	Not given	
Median survival (months)	14.5 (4-22)	6 (1-25)
p-values	None given but described as non-significant	

Table 18 - Hyperfractionated regimens with adjuvant chemotherapy compared to standard radiotherapy – secondary outcomes

	Koca 1996[6]	
	ARM 1	**ARM 4**
No. of patients	10	7
Intervention	STD-RT	HFX-RT + CT
Adverse events		
Acute grade 3	None	1 grade 4 reaction in arm 4
Acute grade 4	None	
Late grade 3	None	
Late grade 4	None	
Rx related deaths	None	None
p-values	None given but described as non-significant	
Quality of life data – Not studied		
Other-clinical response		
Complete Partial Stable Disease Progressive Disease Response Rate (CR + PR) Missing	Reported as tumour response > 50% in 20 patients overall the trial arms and < 50 % in 10 patients. No other information given.	
p-values	None given but described as non-significant	

Table 19 - Hyperfractionated, split-course radiotherapy regimens compared to standard radiotherapy – survival

	Bonner 1998[4]	
	ARM 1	**ARM 2**
No. of patients	34	33
Intervention	STD-RT	SCHFX-RT + CT
Hazard ratios	Not given	
% survival by year 1 year (95% CI) 2 year (95% CI) 3 year (95% CI) 4 year (95% CI) 5 year (95% CI)	Not given	
Median survival (months)	Not given	Not given
p-values	P=0.17	

Table 20 - Hyperfractionated, split-course radiotherapy regimens compared to standard radiotherapy – secondary outcomes

	Bonner 1998[4]	
	ARM 1	**ARM 2**
No. of patients	34	33
Intervention	STD-RT	SCHFX-RT
Adverse events		
Acute grade 3	Pnemonitis G3-4 cases G4-1 case Oesophagitis G3-3 cases Nausea G3-1 case	Pnemonitis G3-4 cases G4-no cases Oesophagitis G3-3 cases Nausea G3-2 cases
Acute grade 4		
Late grade 3		
Late grade 4		
Rx related deaths	1 (pneumonitis)	None
p-values		
Quality of life data – Not studied		
Other-clinical response		
Complete	12%	24%
Partial	9%	21%
Stable Disease	26%	33%
Progressive Disease	35%	3%
Response Rate (CR + PR)	21%	45%
Missing	0%	0%
Regression	18%	18%
p-values	p=0.04	

Table 21 - Hyperfractionated, split-course radiotherapy regimens with adjuvant chemotherapy compared to standard radiotherapy – survival

	Bonner 1998[4]		Wang 1999[8]	
	ARM 1	**ARM 3**	**ARM 1**	**ARM 4**
No. of patients	34	32	30	30
Intervention	STD-RT	SCHFX-RT+CT	STD-RT	SCHFX-RT + CT
Hazard ratios	Not given		Not given	
% survival by year				
1 year (95% CI)	Not given		30	80
2 year (95% CI)			7	23
3 year (95% CI)			0	10
4 year (95% CI)			Not given	Not given
5 year (95% CI)			Not given	Not given
Median survival (months)	Not given	Not given	Not given	Not given
p-values	p=0.27		P=<0.05 for 1,2 and 3-year survival i.e. survival significantly better in arm 4 than arm 1	

Table 22 - Hyperfractionated, split course radiotherapy regimens with adjuvant chemotherapy compared to standard radiotherapy – secondary outcomes

	Bonner 1998[4]		Wang 1999[8]	
	ARM 1	**ARM 3**	**ARM 1**	**ARM 4**
No. of patients	34	33	30	30
Intervention	STD-RT	SCHFX-RT + CT	STD-RT	HFX-RT + CT
Adverse events				
Acute grade 3	Pneumonitis G3-4 cases G4-1 case	Pneumonitis G3-5 cases G4-no cases	Not stated	Overall patients receiving CT in trial: vomiting 70%, nausea 73%, loss appetite 76%, Low wbc 10%, cardiac toxicity 6%, tight chest 6%, weakness 65%.
Acute grade 4	Oesophagitis G3-3 cases G4-no cases	Oesophagitis G3-3 cases G4-1 case	Not stated	
Late grade 3			Not stated	
Late grade 4	Nausea G3-1 case G4-no cases	Nausea G3-7 cases G4-no cases	Not stated	
Rx related deaths	1 (pneumonitis)	None	Not stated	
p-values	None given		Not stated	
Quality of life data – Not studied				
Other-clinical response				
Complete Response	12%	6%		
Partial Response	9%	19%	7%	20%
Stable Disease	26%	53%	57%	73%
Progressive Disease	35%	6%	Not given	Not given
Response Rate (CR + PR)	21%	25%	Not given 64%	Not given 93%
Missing	0%	0%	Not given	Not given
Regression	18%	16%		
p-values	P=0.84			

Table 23 - Combined hyperfractionated/accelerated radiotherapy regimens (CHART) compared to standard radiotherapy - survival

	Saunders 1999[2]	
	ARM 1	**ARM 2**
Number of patients	225	338
Intervention	STD-RT	CHART
Survival		
Hazard ratios	0.78 (95% Confidence Intervals - 0.66-0.94)	
% survival by year		
1 year (95% CI)	55%	63%
2 year (95% CI)	21%	30%
3 year (95% CI)	13%	18%
4 year (95% CI)	8% *	14% *
5 year (95% CI)	7% *	12% *
Median survival (months)	13	16.5
p-values	p=0.009 Results suggest largest benefit for patient with squamous cell histology i.e. 5 year survival 15m (CHART and 7m (STD-RT)	

Table 24 - Combined hyperfractionated/accelerated radiotherapy regimens (CHART) compared to standard radiotherapy – secondary outcomes

	Saunders 1999[2]	
	ARM 1	**ARM 2**
Number of patients	225	338
Intervention	STD-RT	CHART
Adverse effects		
	Initial : dysphagia greater in arm 1 (19% v 3%), radiation pnemonitis greater in arm2 (19% v 10%) Intermediate : Lhermittes sign 8- patients on CHART (no other details given) Late : Pulmonary fibrosis at 2 years grater in arm2 (4% v 16%) (no other details given)	
Treatment related deaths	2	2
p-values	None	
Quality of Life data		
	See table 25	
Other – Clinical Response		
Complete	17%	15%
Partial	36%	46%
Stable Disease	28%	24%
Progressive Disease	11%	11%
Response Rate (CR + PR)	53%	61%
Missing	8%	4%
p-values	None	

Table 25 - Combined hyperfractionated/accelerated radiotherapy regimens (CHART) compared to standard radiotherapy continued – quality of life

	Bailey 1998[25] i.e.Saunders 1999[2]	
	ARM 1	**ARM 2**
Number of patients	141 (63% of all patients i.e. UK patients only)	215 (64% of all patients i.e. UK patients only)
Intervention	STD-RT	CHART
RSCL symptoms – SHORT TERM		
Exploratory data set used to generate hypotheses		
(a) At baseline (before treatment)	No significant differences in presence of symptoms	Significantly more patients reported despondent feeling (p=0.07)
(b) Subject-specific analysis - At 3 months	Significantly more patients reported cough (p=0.11), shortness of breath (p=0.03) and dizziness (p=0.03)	No significant differences in presence of symptoms
(c) Group-based analysis - At day 21	No significant differences in presence of symptoms	Significantly more patients reported sore mouth or pain on swallowing (p=0.002), lack of appetite (p=0.15), pain (p=0.008) and heartburn (p=0.001)
Confirmatory data set used to test hypotheses from exploratory data set		
(a) At baseline (before treatment)	Significantly more patients reported diarrhoea (p=0.01)	Significantly more patients reported difficulty concentrating (p=0.01)
(b) Subject-specific analysis - At 3 months	None of the hypotheses generated in the exploratory dataset were confirmed	n/a
(c) Group-based analysis - At day 21	n/a	Evidence to confirm that sore mouth or pain on swallowing (p=<0.001) and heartburn (p=0.02) significantly greater in this group. No evidence to support that pain or lack of appetite were greater in this group.
Differences between the exploratory and confirmatory data sets overall	Overall there was a significantly greater proportion of patients with borderline or case anxiety/depression in the exploratory data set compared with the confirmatory data set but no differences between interventions	
HADS SCORE (Normal , Borderline or Case) – SHORT-TERM		
Exploratory data set used to generate hypotheses		
(a) At baseline (before treatment)	No significant differences in presence of symptoms	No significant differences in presence of symptoms
(b) At 3 months Subject-specific analysis	No significant differences in presence of symptoms	No significant differences in presence of symptoms
(c) Group-based analysis - At day 21	No significant differences in presence of symptoms	No significant differences in presence of symptoms
Confirmatory data set used to test hypotheses from exploratory data set		
(a) At baseline (before treatment)	No significant differences in presence of symptoms	No significant differences in presence of symptoms
(b) Subject-specific analysis - At 3 months	n/a	n/a
(c) Group-based analysis - At day 21	n/a	n/a
Differences between the exploratory and confirmatory data sets overall	Overall there was a significantly greater proportion of patients with tiredness, sore muscles, depressed mood, nervousness, despondent feelings, restlessness, feeling tense and anxious feelings in the exploratory data set compared with the confirmatory data set but no differences between interventions	
RSCL symptoms– LONG TERM (78% patients completed questionnaire)		
At 1 year (206 patients – 130 CHART, 76 STD)	No significant differences reported	
At 2 years (73 patients – 51 CHART, 22 STD)	No significant differences reported	
HADS SCORE- LONG TERM (74% patients completed questionnaire)		
At 1 year (206 patients – 130 CHART, 76 STD)	No significant differences reported	
At 2 years (73 patients – 51 CHART, 22 STD)	No significant differences reported	

Appendix 12 - Derivation Of Cost Per Lyg Estimates

- Survival Difference was calculated by first deriving a mean value for the reported median survival for the standard therapy arm from the trials where this data was available (Important to note that we used median survival in order to calculate a mean). The mean survival for standard therapy was 50.4 weeks. Secondly a median survival for the intervention groups was determined using the hazard ratio (and there 95% confidence intervals for the range).

  e.g. $M_{CHART} = M_{standard} / HR$; and for the range
  $M_{CHART} = M_{standard/}$upper limit of 95% CI and $M_{CHART} = M_{standard/}$lower limit of 95% CI.

- Costs were annualised using the 3 month estimates from Coyle and Drummond[10], for CHART and standard therapy. 95% CI were constructed using the given standard deviations i.e. 95% CI = 1.96 x Standard Error(SE)

  $$(SE = \frac{\text{Standard Deviation})}{\sqrt{n}}$$

- The costs for standard therapy were applied directly to the accelerated alone regimen using the assumption that costs were identical due to number of fractions being identical although for the accelerated regimen patients attend twice daily but for fewer days (This assumes that there is no difference in 'other' hospital costs due to the treatment or adverse events associated with this treatment)

- The costs for the remaining regimens were calculated using the raw data for radiotherapy costs in Coyle and Drummond[10]. It was assumed that all radiotherapy took place within normal hours (i.e 60 fractions x £19.23, ranges were given for the costs, therefore a range of annualised costs is given). It was assumed again that all 'other' hospital costs would cost the same as conventional therapy. Again this is likely to be an under-estimation since in these regimens there are twice as many fractions and possibly more adverse events. It was not possible to calculate 'other' hospital costs from the data given in the paper.

- Cost per LYG and its 95% confidence intervals was calculated using the mean difference in costs only and not the ranges for the costs, this is because the reported results are then easier to understand and since many assumptions were made for the costs it did not seem unreasonable to use the mean only. 95% confidence intervals were calculated using the 95% confidence intervals of the difference in survival.

  $$\text{i.e. Cost per LYG} = \frac{\text{Mean Cost Difference}}{\text{Difference in Survival}}$$

  $$\text{Cost per LYG} = \frac{\text{Mean Cost Difference}}{\text{Upper limit of Difference in Survival}}$$

$$\text{Cost per LYG} = \frac{\text{Mean Cost Difference}}{\text{Lower limit of Difference in Survival}}$$

For CHART we also considered differences in cost as these were given in the cost-impact study[10]. For the other regimens we did not consider it appropriate to carry out this sensitivity analysis as the values we derived for cost are only approximate estimates and therefore a sensitivity analysis on costs may be misleading.

The following table provides estimates of the cost per QALY using high, low and mid estimates of differences in costs and benefits for CHART compared to the standard radiotherapy regimen.

	Difference in benefits (survival)			
Difference in costs		High	Mid	Low
	High	Not needed	£16,930	**£76,183**
	Mid	£6062	£11,227	£50,520
	Low	**£2980**	£5519	Not needed

The figures highlighted in bold in the table represent the best and worst case scenarios for the CHART regimens and therefore these are the figures represented in the text.

- Costs are hospital costs only and do not include other NHS costs such as community costs or societal and patient costs.