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Abstract

Clinical effectiveness of first-line chemoradiation for adult patients with locally advanced non-small cell lung cancer: a systematic review

T Brown,[1] G Pilkington,[1] A Boland,[1] J Oyee,[1] C Tudur Smith,[2] Y Dundar,[1] E Richards,[3] R Yang[4] and R Dickson[1*]

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Background: The National Institute for Health and Clinical Excellence has issued guidelines on the treatment of non-small cell lung cancer (NSCLC) and recommends that patients with stage IIIA–IIIB disease who are not amenable to surgery be treated with potentially curative chemoradiation (CTX-RT). This review was conducted as part of a larger systematic review of all first-line chemotherapy (CTX) and CTX-RT treatments for patients with locally advanced or metastatic NSCLC. However, it was considered that patients with potentially curable disease (e.g. stage IIIA) are different from those with advanced disease, who are suitable for palliative treatment only, and therefore the results should be reported separately.

Objective: To evaluate the clinical effectiveness of first-line CTX in addition to radiotherapy (RT) (CTX-RT vs CTX-RT) for adult patients with locally advanced NSCLC who are suitable for potentially curative treatment.

Data sources: Three electronic databases (MEDLINE, EMBASE and The Cochrane Library) were searched from January 1990 to September 2010.

Review methods: Inclusion criteria comprised adult patients with locally advanced NSCLC, trials that compared any first-line CTX-RT therapy (induction, sequential, concurrent and consolidation) and outcomes of overall survival (OS) and/or progression-free survival (PFS). The results of clinical data extraction and quality assessment were summarised in tables and with narrative description. Direct meta-analyses using OS data were undertaken where possible: sequential CTX-RT compared with concurrent CTX-RT; sequential CTX-RT compared with concurrent/consolidation CTX-RT; and sequential CTX-RT compared with concurrent CTX-RT with or without consolidation. There were not sufficient data to perform meta-analysis on PFS.

Results: Of the 240 potentially relevant studies that were published post 2000, 19 met the inclusion criteria and compared CTX-RT with CTX-RT. The results from the OS meta-analysis comparing sequential CTX-RT with concurrent CTX-RT appear to show an OS advantage for concurrent CTX-RT arms over sequential arms; this result is not statistically significant [hazard ratio (HR) 0.79; 95% confidence interval (CI) 0.50 to 1.25)]. The results from the OS meta-analysis comparing sequential CTX-RT with concurrent/consolidation CTX-RT appear to show a statistically significant OS advantage for concurrent/consolidation CTX-RT treatment over sequential treatment (HR 0.68; 95% CI 0.55 to 0.83). The results from the OS meta-analysis comparing sequential CTX-RT with concurrent CTX-RT with or without consolidation appear to

show a statistically significant OS advantage for concurrent CTX-RT with or without consolidation over sequential treatment (HR 0.72; 95% CI 0.61 to 0.84).

Limitations: This report provides a summary and critical appraisal of a comprehensive evidence base of CTX-RT trials; however, it is possible that additional trials have been reported since our last literature search. It is disappointing that the quality of the research in this area does not meet the accepted quality standards regarding trial design and reporting.

Conclusions: This review identified that the research conducted in the area of CTX-RT was generally of poor quality and suffered from a lack of reporting of all important clinical findings, including OS. The 19 trials included in the systematic review were too disparate to form any conclusions as to the effectiveness of individual CTX agents or types of RT. The focus of primary research should be good methodological quality; appropriate allocation of concealment and randomisation, and comprehensive reporting of key outcomes, will enable meaningful synthesis and conclusions to be drawn.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

Glossary

Adenocarcinoma Cancer that begins in cells that line certain internal organs and which have glandular (secretory) properties.

Chemo-naive Chemotherapy naive – having received no previous chemotherapy treatment.

Chemoradiation Combined chemotherapy and radiation therapy.

Chemotherapy Treatment with anticancer drugs.

Heterogeneity Between-trial variation.

Histological diagnosis A diagnosis made by examining a sample of tissue or cells.

Intention to treat A method of data analysis in which all patients are analysed in the group that they were assigned to at randomisation regardless of treatment adherence.

Large cell carcinoma A group of lung cancers in which the abnormal cells are large.

Locally advanced disease Stages IIIA/IIIB non-small cell lung carcinoma.

Meta-analysis A quantitative method for combining the results of many trials into one set of conclusions.

Metastasis The spread of cancer from one part of the body to another. Tumours formed from cells that have spread are called 'secondary tumours' and contain cells that are like those in the original (primary) tumour. The plural is metastases.

Non-small cell lung cancer A group of lung cancers that includes squamous cell carcinoma, adenocarcinoma and large cell carcinoma.

Non-squamous cell carcinoma A classification of cancer that includes adenocarcinoma, which begins in the cells that line the alveoli, and large cell carcinoma that begin in types of large cells.

Radiation therapy The use of high-energy radiation from X-rays, neutrons and other sources to kill cancer cells and shrink tumours. Radiation may come from a machine outside the body (external beam radiation therapy) or from material called radioisotopes. Radioisotopes produce radiation and are placed in or near a tumour or near cancer cells. This type of radiation treatment is called internal radiation therapy, implant radiation or brachytherapy. Systemic radiation therapy uses a radioactive substance, such as a radiolabelled monoclonal antibody, that circulates throughout the body. Also called radiotherapy.

Relative risk The proportion of diseased people among those exposed to the relevant risk factor divided by the proportion of diseased people among those not exposed to the risk factor.

Relative risk reduction Alternative way of expressing relative risk. It is calculated as $RRR = (1 - RR) \times 100\%$. The RRR can be interpreted as the proportion of the baseline 'risk' that was eliminated by a given treatment or by avoidance of exposure to a risk factor.

Squamous cell carcinoma Cancer that begins in squamous cells, which are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body and the passages of the respiratory and digestive tracts. Also called epidermoid carcinoma.

List of abbreviations

AE	adverse event
BSC	best supportive care
CALGB	Cancer and Leukemia Group B
CARB	carboplatin
CIS	cisplatin
CI	confidence interval
CT	computerised tomography
CTX	chemotherapy
CTX-RT	chemoradiation
DOC	docetaxel
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ETOP	etoposide
GEM	gemcitabine
Gy	Gray (unit of absorbed radiation dose)
HART	hyperfractionated accelerated radiotheraphy
HR	hazard ratio
HRQoL	health-related quality of life
ITT	intention to treat
KPS	Karnofsky performance status
LUCADA	National Lung Cancer Data Audit
M +	mutation-positive (EGFR)
MCMC	Markov chain Monte Carlo
MTC	mixed-treatment comparison
NICE	National Institute for Health and Clinical Excellence
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PAX	paclitaxel
PFS	progression-free survival
PLAT	platinum (cisplatin or carboplatin)
PS	performance status
RCT	randomised controlled trial
RDI	relative dose intensity
RR	relative risk
RT	radiotherapy
TTP	time to progression
UICC	Union Internationale Contre le Cancer
VBL	vinblastine
VNB	vinorelbine
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Lung cancer is the most common cancer in the world and the second most common cancer diagnosed in the UK after breast cancer. In 2008, there were 40,806 new cases of lung cancer diagnosed in the UK, with 32,546 in England and 2403 in Wales. Lung cancer is rarely diagnosed in people < 40 years of age, and 86% of cases occur in people > 60 years. In both men and women, smoking is the primary cause of lung cancer and prognosis is poor. Early-stage lung cancer is often asymptomatic, with two-thirds of patients diagnosed at a late stage.

Non-small cell lung cancer (NSCLC) accounts for approximately 84% of lung cancer cases. It comprises two main histological subgroups: squamous cell carcinoma and non-squamous cell carcinoma. Squamous cell carcinoma accounts for 33% of all NSCLC cases while non-squamous cell carcinoma (including adenocarcinoma and large cell carcinoma) accounts for 29% of NSCLC cases. Approximately 36% of patients have NSCLC that is 'not otherwise specified', 1% have carcinoma in situ and 1% have bronchioloalveolar carcinoma.

Patients of interest to this review are those with locally advanced NSCLC who are not suitable for curative surgery or radical radiotherapy (RT) but who are suitable for potentially curative treatment with chemoradiation (CTX-RT). In terms of first-line treatment, National Institute for Health and Clinical Excellence (NICE) guidelines recommend CTX-RT as the treatment of first choice for patients with stage II or III NSCLC who are not suitable for surgery. However, how currently available CTX and RT regimens should be optimally combined within concurrent CTX-RT remains unclear.

Objective

The aim of this study was to evaluate the clinical effectiveness of first-line chemotherapy (CTX) in addition to RT (CTX-RT vs CTX-RT) for adult patients with locally advanced NSCLC (stages IIIA and IIIB). This review aimed to identify the optimal combination of CTX and RT for this group of patients. There are four main types of CTX-RT: combined, concurrent, sequential and consolidation. Studies with at least two CTX-RT treatment arms comprising any CTX-RT including concurrent, sequential, induction/concurrent and concurrent/consolidation treatments were eligible for inclusion in our evidence synthesis.

The Assessment Group conducted this review as part of a larger systematic review of all first-line CTX and CTX-RT treatments for patients with locally advanced or metastatic NSCLC. It was the opinion of the members of the clinical panel for the project that patients with potentially curable disease (e.g. stage IIIA) are different from those who are considered only for palliative treatment of more advanced disease and that therefore the results relating to these former patients should be reported separately.

Methods of the systematic review (clinical effectiveness)

Search strategy

Three electronic databases (MEDLINE, EMBASE and The Cochrane Library) were searched for randomised controlled trials (RCTs) and systematic reviews. MEDLINE and EMBASE were searched from January 1990 to September 2010. The Cochrane Library was searched up to July 2010. In addition, the database of the American Society for Clinical Oncology (ASCO) was searched from 1998 to 2011 to identify any relevant trials from conference abstracts.

Inclusion criteria

The systematic review was guided by the general principles recommended in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The results of clinical data extraction and quality assessment are summarised in tables and narrative description.

Patient population

Chemotherapy-naive adult patients with locally advanced NSCLC.

Interventions and comparators

Trials that compared any first-line CTX-RT treatment.

Outcomes

Overall survival (OS) and/or progression-free survival.

Data synthesis

Where appropriate, relative treatment effects for OS were estimated using a standard meta-analysis for head-to-head comparisons between interventions based on intention-to-treat (ITT) analyses. Data limitations meant that further analysis or a mixed-treatment comparison (MTC) was not appropriate.

Results

Of the 240 potentially relevant studies that were published post 2000, 19 met the inclusion criteria of the review. The majority of patients within the trials were male and aged between 53 and 64 years and had stage III adenocarcinoma or squamous cell carcinoma and performance status of 0–1.

Twelve trials compared various regimens of sequential, concurrent and consolidation CTX-RT. Five trials compared different types of RT or CTX, one trial compared RT once daily with RT twice daily, and another trial assessed the addition of weekend CTX. In addition, there were different CTX agents and different radiation doses both across and within trials; number of fractions, schedule, intensity and overall treatment time varied between trials.

The Assessment Group performed several direct evidence comparisons (meta-analysis) using data combining induction, sequential, concurrent and consolidation CTX-RT. The results appear to show no statistically significant evidence to support OS advantage for concurrent CTX-RT over sequential CTX-RT. However, when concurrent/consolidation treatments were compared with sequential treatments, the difference in OS was shown to be statistically significant. When sequential CTX-RT was compared with concurrent CTX-RT with or without consolidation, the latter yielded a statistically significant improvement in OS.

In the trials comparing sequential CTX-RT with concurrent CTX-RT, more patients in the concurrent arms tolerated higher doses of RT. Concurrent/consolidation CTX-RT may be easier to tolerate than induction/concurrent CTX-RT. However, concurrent CTX-RT is associated with greater oesophagus toxicity than sequential CTX-RT.

Conclusions

This review identified that the research conducted in the area of CTX-RT was generally of poor quality and suffered from a lack of reporting of all-important clinical findings, including OS. In addition, there were within- and between-trial variations in treatment protocols including in treatment duration, sequencing and length, RT exposure and type of CTX. These wide variations severely limited the combination of trial

results. The trials were too disparate to form any conclusion as to the optimal individual CTX agent or optimal type of RT.

Meta-analyses conducted as part of this review demonstrated a small but statistically significant improvement in OS in patients receiving concurrent/consolidation CTX-RT compared with sequential CTX-RT and statistically significantly improved OS with the use of concurrent CTX-RT (with or without consolidation) over sequential treatment. However, as noted, the variation in treatment protocols and the changes in the diagnostic criteria and staging used in NSCLC mean that the results of comparisons across these trials and with future trials need to be viewed with caution.

Suggested research priorities

An overall strategy that provides structure and continuity of research in the area of CTX-RT is required to allow for clear conclusions regarding its effectiveness to be drawn. The focus of primary research should be good methodological quality. Appropriate allocation of concealment and randomisation alongside comprehensive reporting of key outcomes such as OS and health-related quality of life (HRQoL) will enable meaningful synthesis and allow clear conclusions to be drawn.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Description of the health problem

Incidence and prevalence

Lung cancer is the most common cancer in the world and the second most common cancer diagnosed in the UK after breast cancer. In 2008, there were 40,806 new cases of lung cancer diagnosed in the UK, with 32,546 in England and 2403 in Wales.[1] Lung cancer is rarely diagnosed in people < 40 years of age, and 86% of cases occur in people > 60 years.[1] *Table 1* provides an overview of lung cancer statistics in the UK. The European age-standardised incidence rate of lung cancer in 2008 was 45.6 per 100,000 population in England and 52.2 per 100,000 population in Wales.[1] The UK incidence rate in men is similar to incidence rates in most of Western Europe and is lower than incidence rates in most of Eastern Europe.[1] The UK incidence rate in women is one of the highest rates in the European Union.[1] There is an increased incidence of lung cancer in individuals from the lowest socioeconomic strata.[2] In 2008, around 65,000 individuals were living with lung cancer in the UK;[1] the majority of these individuals were men.[1]

Causation

Smoking causes around 90% of lung cancer deaths in men and > 80% of lung cancer deaths in women in the UK.[1] Other causes include radon exposure, air pollution, heredity and occupational exposure such as to asbestos and industrial chemicals.[3]

Survival

There were 35,261 lung cancer-related deaths in the UK in 2008.[1] Prognosis is very poor; lung cancer is usually asymptomatic in the early stages, and two-thirds of patients are diagnosed at a late stage when curative treatment is not possible. In total, 27% of male and 30% of female lung cancer patients in England and Wales survive for 1 year; 7% and 9%, respectively, survive to 5 years.[1] According to the National Lung Cancer Data Audit (LUCADA) report[4] for 2006–8, the median survival for individuals with lung cancer in England is 203 days (interquartile range 62 to 545 days).

There are many factors that affect lung cancer survival rates, including smoking status, general health, sex, race and cancer treatments. For example, Asian individuals with lung cancer have a significantly higher percentage survival at 1 and 3 years than white patients, regardless of age.[1]

TABLE 1 UK lung cancer statistics[1]

Lung cancer	Men	Women	Total
Number of new cases (UK 2008)	22,846	17,960	40,806
Rate per 100,000 population[a]	59.4	38.8	47.8
Number of deaths (UK 2008)	19,868	15,393	35,261
Rate per 100,000 population[a]	51.0	32.0	40.3
One-year survival rate (for patients diagnosed 2004–6, England)	27%	30%	–
Five-year survival rate (for patients diagnosed 2004–6, England)	7%	9%	–

a Age-standardised to the European population.

Diagnosis

As noted earlier, lung cancer at an early stage is usually asymptomatic and thus diagnosis is often at a late stage. Unfortunately, two-thirds of patients are diagnosed when the cancer has metastasised. Across England and Wales a significant proportion of each age group presents with late-stage metastatic disease.[4] According to recently updated National Institute for Health and Clinical Excellence (NICE) guidelines,[5] urgent referral for chest radiography should be offered when a patient presents with haemoptysis or any of the following unexplained or persistent (i.e. lasting > 3 weeks) symptoms or signs:

- cough
- chest/shoulder pain
- dyspnoea
- weight loss
- chest signs
- hoarseness
- finger clubbing
- features suggestive of metastasis from a lung cancer (e.g. in brain, bone, liver or skin)
- cervical/supraclavicular lymphadenopathy.

The updated NICE guidelines[5] for the diagnosis and treatment of lung cancer recommend that, if a chest radiograph or chest computerised tomography (CT) scan suggests lung cancer, patients should be offered an urgent referral, usually to a chest physician, who should choose further investigations that give the most information about diagnosis and staging with the least risk to the patient. There are various diagnostic and staging techniques for non-small cell lung cancer (NSCLC) in the UK. Within this diagnostic process there are a number of key issues that need to be considered, including disease staging, performance status (PS), histology and the presence of comorbid disease.

Disease staging

The stage of lung cancer at diagnosis reflects the degree of spread of cancer and is crucially important to determine which patients have potentially curative disease and which do not; this helps to estimate a patient's prognosis. The TNM classification provides a system for staging the extent of cancer. T refers to the size and extent of the primary tumour, N refers to the involvement of the lymph nodes and M refers to the presence of metastases or distant spread of the disease. Recently, changes have been made to the predominantly used Union Internationale Contre le Cancer (UICC) TNM system for classification of NSCLC disease stage[5] (previous UICC versions are available from the American Joint Committee on Cancer). There are several differences in staging between UICC versions 6 and 7 that are specifically relevant to patients with advanced lung cancer. For example, pleural effusion is classed as stage IIIB in version 6 and has been reclassed as stage IV in version 7. *Table 2* shows how the stages from the sixth edition that have been modified compare with the new stages in the seventh edition. *Table 3* shows the stage groupings in the seventh edition of the TNM classification.

Performance status

Performance status is a measure used to quantify cancer patients' general well-being and is used to determine whether or not a patient is fit enough to receive treatment and to assess how much supportive care a patient needs. There are three main scales used to measure PS: the World Health Organization (WHO) PS scale,[6] the Karnofsky PS scale (KPS)[6] and the Eastern Cooperative Oncology Group (ECOG) PS scale.[7] A summary of the WHO PS scale is shown in *Table 4* as this is the most commonly used scale in clinical practice in the UK.[6] A score of 0 on the WHO scale indicates that a patient is completely able to look after him- or herself and a score of 4 shows that a patient requires a lot of support.

TABLE 2 TNM staging of NSCLC in the sixth edition compared with the seventh edition of the UICC classification system

Sixth edition (2002)	Seventh edition (2009)	
TNM stage	TNM stage	Descriptor
T1	T1a	Maximum dimension ≤ 2 cm
	T1b	Maximum dimension 2–3 cm
T2	T2a	Maximum dimension 3–5 cm
	T2b	Maximum dimension 5–7 cm
	T3	Maximum dimension > 7 cm
T4	T3	Additional nodule in same lobe
M1	T4	Additional nodule in ipsilateral different lobe
M1	M1a	Additional nodules in contralateral lung
M1	M1a	Ipsilateral pleural effusion

TABLE 3 Surgical stage groupings in the seventh edition of the TNM classification

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1a, b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a, b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1, T2	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a, b

TABLE 4 World Health Organization PS criteria[8]

Scale	WHO criteria
0	Patient is fully active and more or less the same as before illness
1	Patient is unable to carry out heavy physical work but can do anything else
2	Patient is up and about more than half the day; able to look after him/herself but not well enough to work
3	Patient is in bed or sitting in a chair for more than half the day; needs some help in looking after him/herself
4	Patient is in bed or a chair all the time and needs a lot of looking after

Histology

Histological confirmation (i.e. a diagnosis made by taking a sample of tissue or cells) is an important element of diagnosis because it helps to determine a patient's treatment pathway. However, a proportion of diagnoses are based on clinical examination and radiological investigations alone, without histological evidence. The LUCADA data show that, for England and Wales, histological confirmation of the cancer diagnosis is made in 72% of cases, with wide (regional) variation from 25% to > 85%.[4] Recent NICE guidance for the first-line treatment of NSCLC recommends histological testing and therefore histological testing rates are expected to increase.[5]

There are two main types of lung cancer: NSCLC accounts for approximately 84% of all lung cancers diagnosed and the remaining 15% are small cell lung cancer. The main subtypes of NSCLC are squamous cell carcinoma (33%) and non-squamous cell carcinoma (29%); the latter includes adenocarcinoma (25%) and large cell carcinoma (4%). Approximately 36% of patients are listed as being NSCLC 'not otherwise specified', 1% are carcinoma in situ and 1% are bronchioloalveolar.[9]

Squamous cell carcinoma commonly begins in the bronchi, centrally in the lungs. Adenocarcinoma starts in the periphery of the lungs and can be present for a long time before detection. It is usually the type of lung cancer found in non-smokers and is the most common type seen in women. Large cell carcinomas often occur in the outer regions of the lungs and tend to grow rapidly and spread more quickly than some other forms of NSCLC.[10]

Treatment options for non-small cell lung carcinoma

Figure 1 shows a treatment pathway for patients with NSCLC and estimates of the proportions and numbers of patients with NSCLC along the treatment pathway in England and Wales based on histology and staging data, NICE guidelines[5] and NICE guidance.[10–14] A proportion of patients have small cell disease and recommendations for this group are not discussed in this report.

In total, 30% of patients with NSCLC are diagnosed with stage I–IIIA disease. These patients may be suitable for potentially curative surgery or radical radiotherapy (RT). Surgery for NSCLC consists of lobectomy, pneumonectomy and wedge resection. Approximately 50% of patients undergoing these procedures will relapse and will then be eligible for further treatment. Patients with stage IIIA–IIIB disease who are not amenable to surgery can be treated with potentially curative chemoradiation (CTX-RT). CTX-RT can be delivered in different ways: as induction, sequential, concurrent and/or consolidation CTX-RT. For example, gemcitabine (GEM)-, vinorelbine (VNB)-, docetaxel (DOC)- and paclitaxel (PAX)-based CTX can be used alongside RT.

The majority (70%) of patients with NSCLC have stage IIIB or IV disease and a PS of 0 or 1 at the time of diagnosis. These patients are assessed for their suitability for first-line chemotherapy (CTX); less than half (48%) of patients who are assessed are considered suitable and actually receive treatment. Among those who receive CTX, almost half will respond to treatment and have either a complete or a partial response. Of these patients, a relatively small proportion can go on to have maintenance treatment and only 28% are suitable for second-line CTX.

The majority of patients with NSCLC are diagnosed late and have metastatic or locally advanced disease. Therefore, up to 50% of patients are treated with best supportive care (BSC) alone. During all stages of treatment, patients receive BSC or 'active supportive care' in addition to any anticancer treatment. In the recently published lung cancer guidelines,[5] NICE defines 'supportive care' as 'the multidisciplinary holistic care offered to all patients and their carers throughout the pathway to help them cope with cancer and treatment of it. BSC packages include options for information giving, symptom control and psychological, social and spiritual support. Palliative care provides a similar holistic approach, but is specific to those patients with advanced progressive illness' (p. 98).

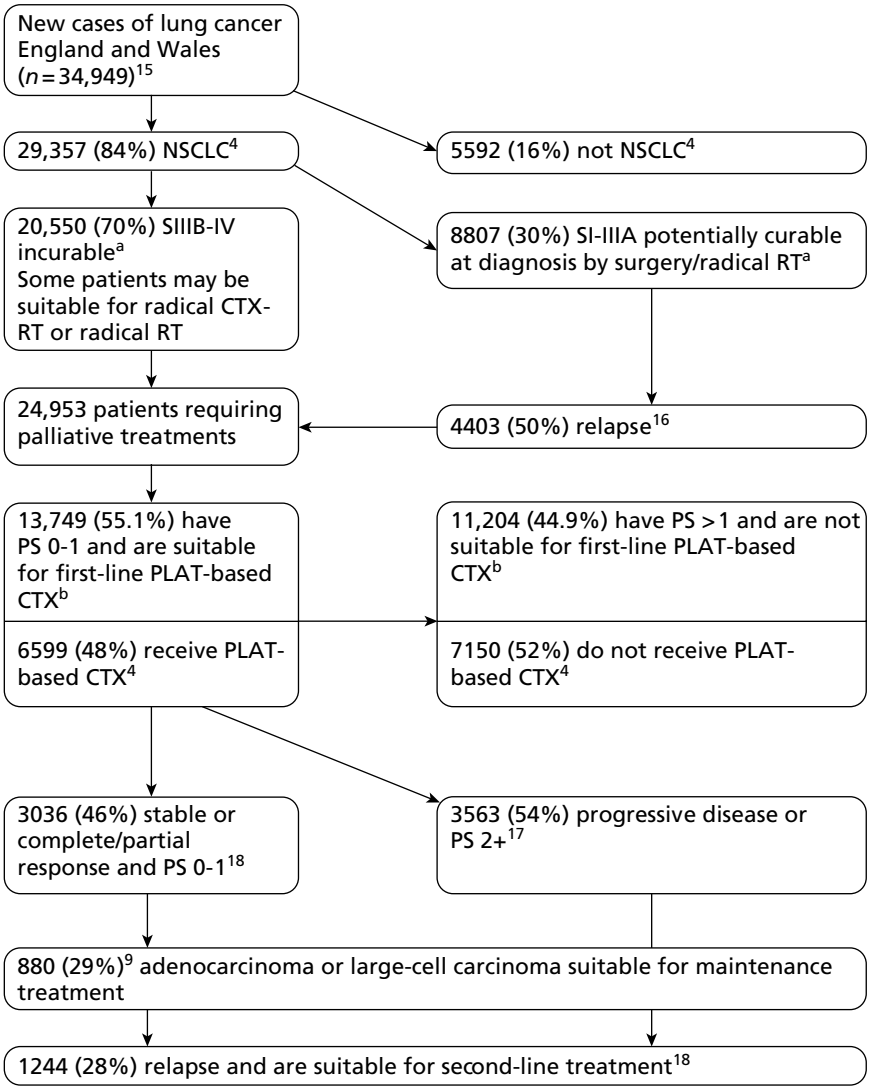

FIGURE 1 Treatment pathway for patients with NSCLC. PLAT, platinum (cisplatin or carboplatin); S, stage. a, M Peak, data from the National Lung Cancer Audit, audit period 2009, personal communication, 2011; b, M Peak, data from the National Lung Cancer Audit, audit period 2008, personal communication, 2011.

Combined chemotherapy and radiotherapy treatment

Radiotherapy is the treatment of cancer with high-energy radiation. RT can be either radical (potentially curative) or palliative. For patients of good PS in whom the disease can be encompassed within a radical RT treatment volume (mainly stage IIIA and selected stage IIIB), high doses of RT at conventional fractionation were the standard treatment with potential curative intent until the 1990s. Developments in RT regimens, including improved techniques and fractionation schedules,[5] coupled with the addition of CTX have improved local control, systemic relapse and overall survival (OS).[19] Radical RT now commonly means potentially curative external beam RT and includes several fractionation schedules, including conventional fractionated RT, split-course RT, hyperfractionated RT, continuous hyperfractionated accelerated RT (CHART) and hyperfractionated accelerated RT (HART). In addition, there have been considerable recent technological advances in RT equipment [e.g. four-dimensional planning to account for tumour movement over the breathing cycle and On-Board Imager® treatment verification (Varian Medical Systems, Palo Alto, CA, USA)] that allow RT to be more accurately delivered to the tumour with less damage to normal tissues.[5] Also, recent innovation has enabled new approaches to be developed, for example stereotactic body RT.[5]

The aim of adding CTX to RT is to improve the cure rate obtained with RT alone; CTX is used as a systemic treatment to control micrometastases and the risk of systemic relapse. In addition, many CTX agents have a radiation-sensitising effect and offer potential benefits in locoregional control.[5] RT is aimed at improving local control of the tumour. CTX-RT is described in different ways depending on the timing of the CTX relative to the RT (*Table 5*).

Compared with RT alone, both sequential and concurrent CTX-RT have shown a 4% improvement in 2-year survival rates.[20,21] A Cochrane meta-analysis[22] of 13 trials (2214 patients) confirmed a statistically significant reduction in risk of death at 2 years with concurrent CTX-RT compared with RT alone, although there was significant heterogeneity across the trials. An update of the Cochrane review[19] compared sequential with concurrent CTX-RT. The authors of the review demonstrated a statistically significant benefit in median survival for concurrent CTX-RT (16–17 months) over sequential CTX-RT (13–15 months). However, the treatment-related mortality was almost twice as high in the concurrent arm and the incidence of acute oesophagitis was 19% in the concurrent arm compared with 3% in the sequential arm. The authors of the Cochrane review[19] recognise that there was considerable heterogeneity related to the frequency of administration and doses of CTX.

Outcome measures

Survival is considered to be the most reliable cancer end point within a randomised controlled trial (RCT) and, when trials can be conducted to adequately assess survival, it is usually the preferred end point. OS is a measure of the time from randomisation to death from any cause; median OS is the point in time at which 50% of people with a condition will have died and 50% are still alive. Year 1 and year 2 survival risk is defined as the probability of survival in intervals of time elapsed from randomisation to year 1 and year 2 respectively.

Many trials also report progression-free survival (PFS) as an intermediate surrogate measure of survival. PFS measures the amount of time between randomisation until tumour progression or death from any cause. In most trials tumour progression is defined using RECIST criteria (Response Evaluation Criteria in Solid Tumors) as at least a 20% growth in the size of the tumour or spread of the tumour since the beginning of treatment with a 5-mm absolute increase in size.[23] Time to progression (TTP) is defined as the time from randomisation until tumour progression (and does not include death). The majority of RCTs measure overall response rate (ORR), which is the proportion of patients who have a response (the tumour shrinks), which can be complete or partial. Stable disease is recorded when there is no response and the tumour does not change in size. Stable disease also means that no new tumours have developed and that the cancer has not spread to any new regions of the body.[24]

Adverse event (AE) rates and health-related quality-of-life (HRQoL) data are also measures of important clinical benefit and provide information on how well patients are able to tolerate CTX treatments. AEs

TABLE 5 Definitions of CTX-RT

Terms	Description
Radical RT	All RT that is not palliative in intent. Minimum dose of 50 Gy in 25 daily fractions or its radiobiological equivalent
Combined CTX-RT	Treatment given to patients eligible for potential curative RT at presentation; the treatments are given either sequentially or concurrently
Concurrent CTX-RT	CTX given on the same days as RT treatment
Sequential CTX-RT	CTX given before a course of RT but not during RT
Consolidation CTX-RT	CTX given subsequent to RT
Induction CTX	CTX given before CTX-RT

within trials are graded for severity (1–4), and usually the more severe events at grades 3 and 4 are of interest to clinicians. These are discussed in more detail in *Chapter 3* (see *Adverse events*).

In advanced NSCLC, CTX-RT treatment is also given in an effort to improve HRQoL. Commonly used HRQoL tools within NSCLC trials include the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30[25] and the lung cancer-specific module QLQ-LC13,[26] the Lung Cancer Symptom Scale (LCSS)[27] and the Functional Assessment of Chronic Illness Therapy – Lung (FACT-L) questionnaire.[28] The European Quality of Life-5 Dimensions (EQ-5D)[29] is a standardised generic instrument for measuring HRQoL that may be used in lung cancer trials. It provides a utility score for health and a self-rating of HRQoL. AEs, both from the disease itself and from CTX, have a considerable impact on HRQoL.[30]

Despite HRQoL being both a vitally important measure of a patient's general emotional, physical and mental well-being and a very relevant measure of the 'success' of CTX treatment, because advanced-stage NSCLC is not curable, only a minority of trials address HRQoL issues.

Current UK guidelines and guidance

The National Institute for Health and Clinical Excellence produces clinical guidance and guidelines recommending appropriate treatments and care for people with NSCLC; NICE issues recommendations based on the best available clinical effectiveness and cost-effectiveness evidence. Comprehensive guidelines[31] on the management of patients with lung cancer published by NICE in 2005 concluded that sequential CTX-RT is more beneficial than RT alone for patients with locally advanced NSCLC. The clinical evidence available appeared to support the use of concurrent CTX-RT, but the results of further clinical efficacy studies were required to ensure that informed decision-making could take place.

NICE guidelines[5] on the diagnosis and treatment of lung cancer were updated in 2011. The updated guidelines state that CTX-RT is now an established approach to treatment, with curative intent of patients with NSCLC when surgery is not suitable, and the potential benefit in survival needs to be balanced with the risk of additional toxicities. Current NICE guidelines[5] recommend that CTX-RT is the treatment of first choice for patients with stage II and stage III cancer who are not suitable for surgery; however, how currently available CTX and RT regimens should be optimally combined within concurrent CTX-RT remains unclear.

Rationale for this review

Given the advances in first-line treatment of NSCLC it was felt that an updated review was required. The Assessment Group conducted this review as part of a larger systematic review[32] of all first-line CTX and CTX-RT treatments for patients with locally advanced or metastatic NSCLC. It was the opinion of the members of the clinical panel for the project that patients with potentially curable disease (e.g. stage IIIA) are different from those who are considered only for palliative treatment of more advanced disease and therefore that the results relating to these former patients should be reported separately.

Chapter 2 Definition of the decision problem

Decision problem

The population of interest is adult patients who are CTX naive, with locally advanced NSCLC.

Any first-line CTX-RT therapy (induction, sequential, concurrent or consolidation) was included. The Assessment Group did not place any restrictions on the type of CTX drug or RT included in the review.

The primary outcome was OS.

Secondary outcomes included the following:

- PFS
- survival risk at year 1 and year 2
- ORR
- AEs
- HRQoL.

Overall aim and objective of the assessment

The objective of the assessment is to evaluate the clinical effectiveness of first-line CTX-RT for adult patients with locally advanced NSCLC. This review aims to identify the optimal combination of CTX and RT for this group of patients.

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing effectiveness

Identification of trials

A comprehensive search strategy was developed; search terms included a combination of index terms (e.g. non-small cell lung carcinoma) and free-text words (e.g. lung cancer or lung tumour or lung carcinoma). The search of MEDLINE and EMBASE was restricted to papers with abstracts published in the English language. MEDLINE was searched from January 1990 to March Week 3 2009 and EMBASE was searched from January 1990 to Week 13 2009. The Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials and Health Technology Assessments) was searched in Issue 3, July 2010. An updated search was performed of MEDLINE and EMBASE to identify trials published up until September 2010. All references were exported to the EndNote® reference database (version X4; Thomson Reuters, CA, USA). Details of the search strategies are available in *Appendix 1*. The Liverpool Reviews and Implementation Group (LRiG) team was expanded prior to searching to include clinicians with relevant experience in specialist CTX-RT treatment options.

The protocol was revised to exclude trials that had been published before 2000 because of the large numbers of references identified by the original searches and, more importantly, to reflect recent advances in CTX and RT treatments (e.g. third-generation CTX drugs and HART).

The Assessment Group carried out a number of targeted searches to ensure the completeness of the review, including in the database of the American Society for Clinical Oncology (ASCO) and on the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) websites.

A key review of CTX treatments for patients with NSCLC by Clegg *et al.*[33] was searched for relevant trials. An updated Cochrane review[19] of concurrent CTX-RT has recently been published and communication with the lead author (Noelle O'Rourke) has ensured that all trials relevant to this review have been included. Reference lists of included trials were also searched to identify any further relevant trials.

Inclusion and exclusion criteria

The citations identified by the search strategy were assessed for inclusion; reviewers independently screened all the titles and abstracts identified by electronic searching of MEDLINE and EMBASE and The Cochrane Library (Issue 3, July 2010). The search of MEDLINE and EMBASE was updated to September 2010. Potentially relevant references were obtained as full-text copies and each reference was assessed independently by two reviewers using the inclusion criteria outlined in *Table 6*. The inclusion/exclusion assessment by each reviewer was recorded on a pretested, standardised form.

Data extraction strategy

Data extraction forms were developed and piloted on a sample of included trials. Data on trial design, population characteristics and outcomes were extracted by one reviewer and independently checked for accuracy by a second reviewer. Microsoft Access® software (Microsoft Corporation, Redmond, WA, USA) was used to store extracted data from the included trials. *Appendix 2* contains details of the data extraction.

Critical appraisal strategy

All included trials were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination guidance for undertaking reviews in health care[34] and adapted to reflect the characteristics of patients with NSCLC. Data relating to quality assessment were extracted by one reviewer

TABLE 6 Inclusion criteria (clinical effectiveness) based on the decision problem

Patient population	CTX-naive adult patients with locally advanced NSCLC
Intervention	Any first-line CTX-RT
Comparator	Any first-line CTX-RT
Outcomes	OS and/or PFS estimates
Study design	RCTs

and independently checked for accuracy by a second reviewer. *Appendix 3* contains the trial quality assessment extraction details. Where necessary, any disagreements between reviewers were discussed in consultation with a third reviewer to achieve consensus.

Evidence synthesis

The trends in locally advanced NSCLC treatment in the UK indicate that concurrent CTX-RT has emerged as the standard of care in the NHS.[19,35] However, given the wide range of CTX-RT options, the optimum timing, dosing and choice of systemic agents to achieve the best therapy remain controversial and are subject to ongoing debate. For instance, two recent reviews/meta-analyses[19,35] that evaluated concurrent and sequential CTX-RT schedules reported similar findings in terms of OS but their conclusions on whether or not concurrent CTX-RT should remain a standard of care in locally advanced NSCLC were different. The Aupérin *et al.*[35] review concluded that concurrent CTX-RT should remain a standard of care for patients with locally advanced disease but the authors of the Cochrane review[19] concluded that the evidence base was weak.

In addition, most of the clinical trials[19,35] that have led to concurrent CTX-RT becoming the standard of care have restricted enrolment to patients with good PS, limited weight loss and adequate lung function. Meanwhile, patients who do not meet these criteria are treated with low doses of CTX-RT, sequential CTX-RT, induction/concurrent CTX-RT or concurrent/consolidation CTX-RT. Despite evidence from these reviews,[19,35] it is not immediately apparent what conclusions can be drawn from the clinical evidence regarding the relative efficacy of different CTX-RT treatments as neither of the reviews compared concurrent, sequential, induction/concurrent and concurrent/consolidation options.

Data from eligible studies were synthesised to estimate relative treatment effects. The aim of this evidence synthesis was to identify the best treatment options for the management of locally advanced NSCLC in terms of the optimal timing and sequencing of CTX-RT. Studies with at least two CTX-RT treatment arms comprising any CTX-RT including concurrent, sequential, induction/concurrent and concurrent/consolidation treatments were eligible for inclusion in our evidence synthesis.

The Assessment Group planned analyses using standard meta-analyses and mixed-treatment comparison (MTC) where sufficient clinically and statistically homogeneous data were available from the included studies. The primary outcome for the evidence synthesis was OS, defined as time from randomisation to death of any cause. Planned secondary outcomes included PFS (defined as time from date of randomisation to the earliest sign of disease progression or death from any cause).

Direct evidence synthesis

All planned analyses were based on intention-to-treat (ITT) populations where possible. Where appropriate, standard meta-analyses were undertaken for each pair-wise treatment comparison using the 'metan' command within Stata version 9.2 (StataCorp LP, College Station, TX, USA). Where appropriate, for time-to-event outcomes (OS and PFS) the trial-level estimate of log hazard ratio (HR) and its variance were extracted directly from trial publications if available. In the absence of direct estimates from published papers, previously reported methods that used published data such as Kaplan–Meier survival curves or log-rank statistics were used to estimate the required trial-level log HR and its variance.[36,37] A random-effects

(frequentist) inverse-variance weighted approach was used to pool estimates of log HR across trials. We assessed statistical heterogeneity by considering the chi-squared test for heterogeneity, with a 10% level of significance, and the I^2 statistic, with a value of 50% representing moderate heterogeneity.[38,39]

Mixed-treatment comparison: direct and indirect comparisons

As trials conducting head-to-head comparisons of all treatments under evaluation were not available or sparse, the possibility of conducting an indirect comparison was investigated by the Assessment Group. This approach fulfils the objective of providing simultaneous comparison of all of the relevant treatment alternatives and can provide information about the associated decision uncertainty or sufficient information for economic evaluation. Hence, for the purposes of decision-making, it was planned that a Bayesian MTC framework would be adopted to synthesise information on all technologies simultaneously using Markov chain Monte Carlo (MCMC) methods to estimate the posterior distributions for our outcomes of interest. The MCMC simulation begins with an approximate distribution and, if the model is a good fit to the data, the distribution converges to the true distribution. The MTC analysis allows for the synthesis of data from direct and indirect comparisons and allows for the ranking of different treatments in order of efficacy and estimation of the relative treatment effect of competing interventions. This approach assumes 'exchangeability' of treatment effect across all included trials, such that the observed treatment effect for any comparison could have been expected to arise if it had been measured in all other included trials. Exchangeability would be judged through examination of the trial populations and comparability of outcomes in the common treatment group facilitating the comparison. Inconsistency in the treatment effects between pair-wise comparisons was planned to be investigated by comparing the direct and indirect evidence together with the 95% confidence intervals (CIs).

As with all meta-analyses, MTC may be conducted using either fixed- or random-effects models. Random-effects models allow for the possibility that the true treatment effect may differ between trials. In our analyses, random-effects models would be used throughout. Model fit would be assessed based on residual deviance and deviance information criteria. Adjustment for multiarm trials would be performed as estimates of relative treatment effects from trials with more than two treatment arms will be correlated because of their joint dependence on the reference treatment arm.

In each MCMC simulation we planned to rank the absolute log HR and then use it to calculate the probability that each treatment was best across all simulations.[40,41] If a treatment is statistically significantly better than all other treatments in the MTC, the probability of it being the most effective treatment will be at least 95%. A probability $< 95\%$ indicates that there is at least one other treatment that is not significantly different to the 'best' treatment (at the 5% level). Use of a non-informative (flat prior) normal distribution was planned for the log HR and log relative risk (RR) of each relative comparison; thus, the observed results are completely influenced by the data and not the choice of prior.

Where appropriate, WinBUGS version 1.4 statistical software[42] (MRC Biostatistics Unit, Cambridge, UK) would be used for the MTC analysis by adapting code (presented in *Appendix 4*) from the Multi-parameter Evidence Synthesis Research Group.[43] It was planned to use two chains to ensure that model convergence was met after 90,000 iterations with a burn-in of 10,000. Formal convergence of the models would be assessed using trace plots and the Gelman–Rubin approach[44] and through inspection of the history plots.

Results of the review of clinical effectiveness

Quantity of research available

As shown in *Figure 2*, the electronic searches identified 5378 citations (*Table 7* describes in detail the results of the database searching). Initial screening identified 330 potentially relevant references; these were obtained as full-text copies and the 240 references that were published post 2000 were assessed for eligibility for inclusion. Overall, 19 trials were included that compared different regimens of CTX-RT. The

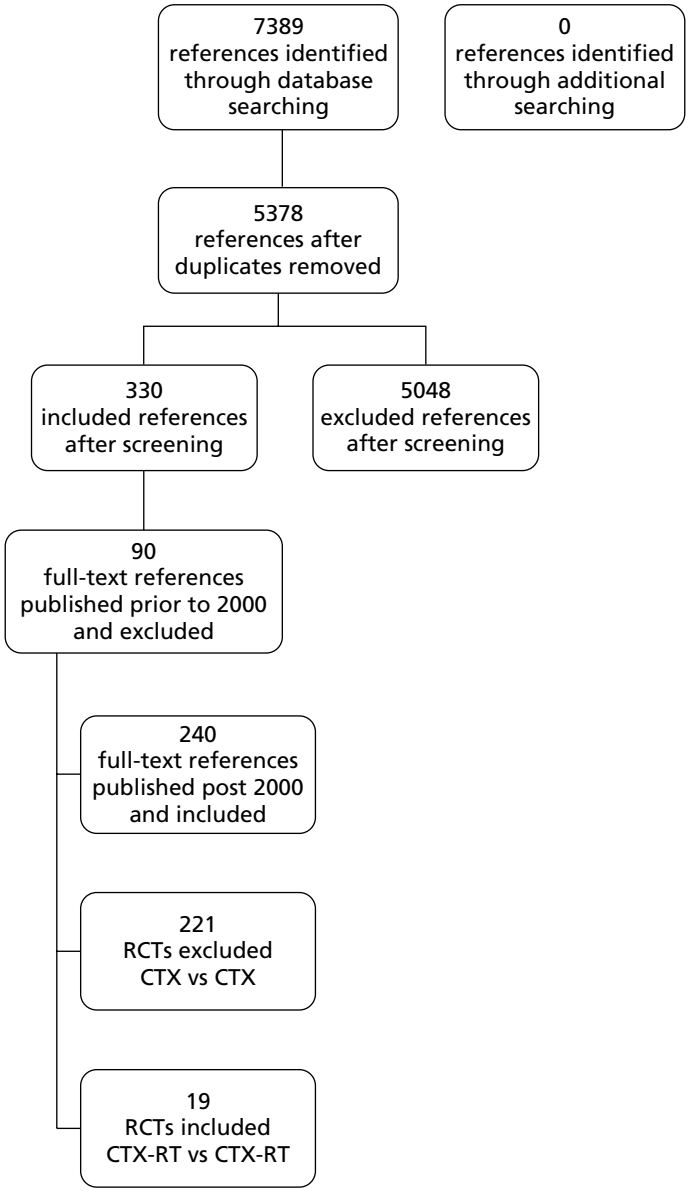

FIGURE 2 Flow diagram of inclusion of CTX-RT trials.

initial search identified a relatively large number of 'hits' because this review was part of a more extensive systematic review[32] that examined CTX compared with CTX as well as CTX-RT compared with CTX-RT.

Assessment of effectiveness

In total, 19 RCTs met the inclusion criteria of the systematic review and compared CTX-RT with CTX-RT.[45–63]

Quality

The results of the methodological quality assessment of trials are presented in *Table 8*. Overall methodological quality of included trials was poor, with nearly all trials failing to report relevant methodology; in particular, methods of randomisation, allocation concealment and blinding were inadequately described.

Only two RCTs[45,46] provided sufficient information regarding randomisation methods. Random assignment was performed centrally in five trials[45,47–50] and so allocation concealment was assessed as adequate in these trials. Another trial used randomisation by envelope to conceal allocation.[51] Eighteen trials

TABLE 7 Results of database searches

Database	Dates	Number	Deduplicated	First screen	Second screen	2000–10	CTX-RT vs CTX-RT
MEDLINE	1990–March Week 3 2009	2594	3848	329	265	175	11
EMBASE	1990–Week 13 2009	3034					
MEDLINE	2009–August Week 3 2010	316	455	35	34	34	5
EMBASE	2009–Week 34 2010	370					
Cochrane Central Register of Controlled Trials	2000–Issue 3 of 4, July 2010	1034	1034	174	31	31	3
Cochrane Database of Systematic Reviews	2000–Issue 3 of 4, July 2010	4	4	0	0	0	0
Database of Abstracts of Reviews of Effects	2000–Issue 3 of 4, July 2010	22	22	0	0	0	0
Health Technology Assessment	2000–Issue 3 of 4, July 2010	15	15	0	0	0	0
Total number of references		7389	5378	538	330	240	19
Total number of RCTs							19

clearly reported the number of participants randomised.[45–59,61–63] All trials reported details of participant comparability at baseline.

Six trials[48,49,52–55] reported imbalance between trial groups at baseline; these were assessed as achieving partial comparability. Two trials[54,55] reported significant imbalance between treatment groups for baseline disease. In one trial[55] 62% of patients had stage IIIB disease in the concurrent GEM plus carboplatin (CARB)-RT arm compared with 32% of patients in the concurrent PAX plus CARB-RT arm. In the trial by Belderbos *et al.*,[54] 47.4% of the patients in the sequential CTX-RT arm had stage IIIB disease compared with 63.8% in the concurrent CTX-RT arm.

All trials reported eligibility criteria. One trial[56] reported details of co-interventions; however, it was unclear how many patients in each treatment arm had received any of the co-interventions. Two trials[49,51] were reported as 'open' and it was assumed that assessors, administrators and participants were not blinded to treatment; blinding was not stated in the remaining 17 trials. Over 80% of patients were assessed in 18 trials.[45–59,61–63] Fourteen trials[45–55,61–63] reported reasons for withdrawals, two trials[57,58] failed to report this and in three trials[56,59,60] there were no withdrawals. Six trials[46,48,51,54,59,61] used an ITT approach and assessed all participants according to the groups to which they were randomised. The trial by Dasgupta *et al.*[56] intended to exclude non-completers from analyses; however, there were no non-completers and so all patients were assessed.

Two trials[54,58] intended to measure HRQoL. In the trial by Belderbos *et al.*[54] it is not clear whether or not HRQoL was measured as it was not reported, and in the trial by Nyman *et al.*[58] HRQoL outcomes were measured and are to be reported in a future publication.

Five of the 19 trials were closed prematurely for the following reasons: confirmation of the benefit of concurrent CTX-RT,[52] poor accrual,[54] poor accrual due to administrative problems,[45] high rate of serious

TABLE 8 Quality assessment

	Randomisation			Baseline comparability				Blinding				Withdrawals			
Reference ID	Truly random	Allocation concealment	Number stated	Presented	Achieved[a]	Eligibility criteria specified	Co-interventions identified[b]	Assessors	Administration	Participants	Procedure assessed	> 80% in final analysis	Reasons stated	ITT	Other outcomes
Jeremic 2001[63]	NS	NS	✓	✓✗	NS	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Komaki 2002[50]	NS	✓	✓	✓	NS	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Schild 2002[62]	NS	NS	✓	✓	✓	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Vokes 2002[47]	NS	✓	✓	✓	NS	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Zatloukal 2004[51]	NS	✗	✓	✓	✓	✓	NS	✗	✗	✗	NA	✓	✓	✓	✗
Belani 2005[52]	NS	NS	✓	✓	✓✗	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Fournel 2005[49]	NS	✓	✓	✓✗	✓✗	✓	NS	✗	✗	✗	NA	✓	✓	✗	✗
Reinfuss 2005[46]	✓	NS	✓	✓	NS	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Dasgupta 2006[56]	NS	NS	✓	✓	NS	✓	✓✗	NS	NS	NS	NS	✓	NA	✗[c]	✗
Gouda 2006[59]	NS	NS	✓	✓	✓	✓	NS	NS	NS	NS	NS	✓	NA	✓	✗

	Randomisation			Baseline comparability				Blinding				Withdrawals			
Reference ID	Truly random	Allocation concealment	Number stated	Presented	Achieved[a]	Eligibility criteria specified	Co-interventions identified[b]	Assessors	Administration	Participants	Procedure assessed	> 80% in final analysis	Reasons stated	ITT	Other outcomes
Belderbos 2007[54]	NS	NS	✓	✓	✓✗	✓	NS	NS	NS	NS	NS	✓	✓	✓	✓
Vokes 2007[48]	NS	✓	✓	✓✗	✓✗	✓	NS	NS	NS	NS	NS	✓	✓	✓	✗
Liu 2008[53]	NS	NS	✓	✓	✓✗	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Socinski 2008[55]	NS	NS	✓	✓	✓✗	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Berghmans 2009[45]	✓	✓	✓	✓	NS	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Crvenkova 2009[57]	NS	NS	✓	✓✗	✓	✓	NS	NS	NS	NS	NS	✓	✗	NS	✗
Nyman 2009[58]	NS	NS	✓	✓	NS	✓	NS	NS	NS	NS	NS	✓	✗	✗	✓
Zhu 2009[60]	NS	NS	NS	✓✗	NS	✓	NS	NS	NS	NS	NS	NS	NA	NS	✗
Movsas 2010[61]	NS	NS	✓	✓	NS	✓	NS	NS	NS	NS	NS	✓	✓	✓	✗

✓, item adequately addressed; ✗, item not adequately addressed; ✓✗, item partially addressed; NA, not applicable; NS, not stated.

a When no *p*-values are reported the trial was assessed as NS.

b This is second-line CTX and/or palliative RT.

c Although trial intended to exclude non-completers from analysis all patients completed treatment.

AEs in the induction/concurrent CTX-RT arm[55] and slow accrual coupled with interim analysis results that demonstrated a statistically significant difference in survival in favour of the concurrent CTX-RT arm.[51] One trial experienced slow accrual that led to a reduction in the target number of participants recruited.[62]

Trial characteristics

Trial characteristics are presented in *Appendix 6*. The 19 trials were published between 2001 and 2010. Of the 13 multicentre trials, three have international centres.[45,54,61] There were seven Phase II[47,50,52,54,55,58,61] and six Phase III trials[45,48,49,56,62,63] and six trials in which the phase is unclear.[46,51,53,57,59,60] Eight trials[47,48,50,51,54,55,62,63] were funded by research grants, four trials[49,52,58,61] were funded by pharmaceutical companies and the funding source was not stated in seven trials.[45,46,53,56,57,59,60] Five trials[47,48,58,62,63] were sufficiently powered to evaluate the primary outcome of each trial, which included TTP, median OS, response rate and 2-year survival rate. Five trials[45,49,51,54,61] were inadequately powered and the power of nine trials[46,50,52,53,55–57,59,60] was unclear. Median follow-up of patients ranged from 16.5 to 60 months.

Details of trial interventions are presented in *Appendix 7*. Concurrent CTX is defined as CTX given on RT treatment days (whether before or after each fraction of RT). Sequential CTX-RT is defined as CTX given before or after a course of RT but not during. Consolidation CTX-RT is defined as CTX given subsequent to RT, and induction CTX-RT is defined as CTX given prior to RT.

Four trials[46,51,54,60] compared sequential with concurrent CTX-RT, four trials[49,52,56,57] compared sequential with concurrent/consolidation CTX-RT, three trials[48,50,59] compared induction/concurrent CTX-RT with concurrent CTX-RT and two trials[45,52] compared induction/consolidation CTX-RT with concurrent/consolidation CTX-RT. The remaining six trials[47,55,57,58,61,62] could not be grouped for comparison as they compared a variety of different CTX-RT regimens.

Different CTX agents were used both across and within trials. It is worth noting that GEM, PAX and VNB were used by a similar number of trials, whereas DOC was used by relatively few trials. Etoposide (ETOP) plus platinum (cisplatin or carboplatin) (PLAT) was used in seven trials.[49,50,56,57,61–63]

Radiation doses, number of fractions, schedule, relative dose intensity (RDI) and overall treatment time also varied between and within trials. Details of RDI are presented in *Appendix 8*. Twelve trials[45,46,49–56,60,61] reported details of actual treatment received including median time to complete treatment, percentage of patients who completed treatment as per protocol and details of reductions and delays in CTX and RT. A sample of the within-trial differences that are demonstrated to be statistically significantly different are discussed here.

In the trial by Fournel *et al.*,[49] 88% of patients in the concurrent CTX-RT arm received at least 60 Gy RT, compared with 59.4% in the sequential CTX-RT arm ($p < 0.001$); 54% received two planned cycles of consolidation CTX, 7% received only one course and 39% received no consolidation CTX. In the Zatloukal *et al.* trial,[51] only 58% of patients in the sequential CTX-RT group completed four courses of CTX, compared with 83% in the CTX-RT concurrent group ($p < 0.0007$), and only 64% of the sequential CTX-RT group received RT, compared with 94% of concurrent CTX-RT group ($p = 0.0002$). The required time for completing treatments was statistically significantly different between the two groups in the trial by Zhuan and Wu;[60] the concurrent CTX-RT group took, on average, 31 days less than the sequential CTX-RT group to complete treatment ($p = 0.05$).

In the trial by Reinfuss et al.,[46] treatment was administered to 75% of patients in the concurrent CTX-RT arm on average, compared with 96.7% of participants in the sequential CTX-RT arm; the difference is statistically significant (log-rank test, $p < 0.01$). The only difference in treatment between the trial groups was the sequence of CTX and RT. Reported toxicity was significantly higher in the concurrent CTX-RT group than in the sequential CTX-RT group. Because of this toxicity, treatment was not completed in 21.4% of participants in the concurrent CTX-RT arm compared with 2.2% in the sequential CTX-RT arm.

It appears that the percentage of patients who completed treatment, and a higher dose intensity, was higher for all three CTX drugs regimens in the concurrent/consolidation CTX-RT arm than in the induction/concurrent CTX-RT arm of the trial by Berghmans *et al*.[45] Significantly fewer patients completed 7 weeks of CTX in the induction/concurrent CTX-RT arm than in the concurrent/consolidation CTX-RT arms of the trial by Belani *et al*.[52]

In the trial by Movsas *et al.*,[61] in which patients received consolidation with either GEM or GEM/DOC after identical CTX-RT, 90.6% received all three planned cycles of GEM, compared with 68.8% who received all three cycles of GEM/DOC.

In the trial by Socinski *et al.*,[55] 87.2% completed therapy to at least 74 Gy in the PAX plus CARB-RT arm, compared with 78.3% in the GEM plus CARB-RT arm. Rates of compliance with induction CTX, initiation and completion of concurrent CTX-RT and average dose and completion of thoracic RT were all higher in the PAX plus CARB-RT arm than in the GEM plus CARB-RT arm (this arm was closed prematurely because of the high rate of grade 4/5 pulmonary toxicity).

Patient characteristics

Details of patient characteristics are given in *Appendix 9*. The inclusion/exclusion criteria adopted by each of the trials are presented in *Appendix 10*. The number of patients randomised to trial arms ranged from 20[59] to 184.[48] More than 50% of patients within the trials were male, with a median age of 40–64 years. With the exception of three trials,[45,50,54] all trials included patients with disease stage IIIA or IIIB only. All but seven trials[49,51,53,54,56,60,61] specifically excluded pleural effusions (see *Appendix 10*). The majority of patients within each trial had either adenocarcinoma or squamous cell carcinoma, and three trials[46,48,63] failed to report details describing patient histology. In the majority of trials PS ranged from 0 to 1 [using a variety of PS criteria: ECOG, the Cancer and Leukemia Group B (CALGB)[48], WHO] or from 60 to 100 (KPS). One trial[51] included a small percentage of patients with ECOG PS 2 and one trial[63] included a small percentage of patients with KPS 50.

Outcomes

Trial outcomes are presented in *Table 9*. Across the trials, median OS ranged from 12 to 29.5 months (16 trials), survival rate ranged from 37% to 80% at 1 year (14 trials) and from 14.3% to 66.6% at 2 years (16 trials). Across the trials, median PFS ranged from 5.4 to 14.9 months (11 trials) and median TTP ranged from 7.3 to 13.3 months (two trials). Across the trials, tumour ORR ranged from 33% to 88% (14 trials).

Results of evidence synthesis

Overall, population data describing just over 2000 patients in the 19 trials were eligible for consideration as part of the Assessment Group's approach to evidence synthesis. Detailed characteristics of all included trials are described in *Appendix 6* and are also presented in the appendices. The Assessment Group investigated the possibility of conducting both meta-analysis and MTC analysis using the large quantity of trial data available. The Assessment Group concluded that the data available were heterogeneous: there were variations in CTX agents and different RT doses both across and within trials; number of fractions, schedules, intensity and overall treatment time also varied between trials. In summary, the 19 trials were disparate in terms of the interventions and comparators being compared (*Table 10*) and comprised eight distinct comparisons. As such, the conduct of a MTC was considered to be inappropriate. Direct meta-analysis using OS data was undertaken where possible: sequential CTX-RT compared with concurrent CTX-RT; sequential CTX-RT compared with concurrent/consolidation CTX-RT and sequential CTX-RT compared with concurrent CTX-RT with or without consolidation. The Assessment Group was unable to undertake any meta-analysis on PFS because of limited data.

TABLE 9 Trial outcomes

Reference ID	Treatment	Median OS			Median PFS			Survival 1 year		Survival 2 years		Tumour ORR	
		Months	95% CI	HR (95% CI)	Months	95% CI	HR (95% CI)	%	95% CI	%	95% CI	%	95% CI
Jeremic 2001[63]	CTX + (HFX)RT days 1–5	20	NR	NR	NR	NR	NR	80	NR	47	NR	85	NR
	CTX + (HFX)RT days 1–7	22	NR	NR	NR	NR	NR	78	NR	49	NR	88	NR
Komaki 2002[50]	CTX → CTX + RT	16.4	NR	NR	9.4	NR	NR	63	NR	39	NR	73	NR
	CTX + (HFX)RT	15.5	NR	NR	8.2	NR	NR	58	NR	32	NR	71	NR
Schild 2002[62]	CTX + RT (2× daily)	14	NR	NR	9.4	NR	NR	37	29 to 47	47	NR	NR	NR
	CTX + RT (4× daily)	15	NR	NR	9.6	NR	NR	40	32 to 50	50	NR	NR	NR
Vokes 2002[47]	CTX (GEM + CIS) → CTX + RT	18.3	13.8 to 23.6	NR	8.4	NR	NR	68	56 to 79	37	NR	74	60 to 86
	CTX (VNB + CIS) → CTX + RT	14.8	12 to 19.5	NR	9.1	NR	NR	62	50 to 75	29	NR	67	52 to 80
	CTX (PAX + CARB) → CTX + RT	17.7	12.4 to 24.7	NR	11.5	NR	NR	65	53 to 78	40	NR	73	57 to 85
Zatloukal 2004[51]	CTX + RT	16.6.	NR	0.61 (0.39 to 0.93)	11.9[a]	NR	NR	69.2	NR	34.2	NR	80	62 to 98
	CTX → RT	12.9	NR	NR	8.5[a]	NR	NR	53	NR	14.3	NR	47	33 to 61
Belani 2005[52]	CTX → RT	13	NR	NR	9.0	NR	NR	57	NR	30	NR	NR	NR
	CTX → CTX + RT	12.7	NR	NR	6.7	NR	NR	53	NR	25	NR	NR	NR
	CTX + RT → CTX	16.3	NR	NR	8.7	NR	NR	63	NR	31	NR	NR	NR
Fournel 2005[49]	CTX → RT	14.5	8.3 to 27.4	NR	NR	NR	NR	59.8	50 to 69	26.5	17.9 to 35.0	54	NR
	CTX + RT → CTX	16.3	5.8 to 34.8	NR	NR	NR	NR	60.4	50.8 to 69.9	39.3	29.7 to 48.9	49	NR

Reference ID	Treatment	Median OS			Median PFS			Survival 1 year		Survival 2 years		Tumour ORR	
		Months	95% CI	HR (95% CI)	Months	95% CI	HR (95% CI)	%	95% CI	%	95% CI	%	95% CI
Reinfuss 2005[46]	CTX → CT	NR	NR	NR	NR	NR	NR	NR	NR	26.7	NR	NR	NR
	CTX + RT	NR	NR	NR	NR	NR	NR	NR	NR	33.3	NR	NR	NR
Dasgupta 2006[56]	CTX → RT	NR	NR	NR	NR	NR	NR	88.4	NR	57	NR	65.7	NR
	CTX + R	NR	NR	NR	NR	NR	NR	86.1	NR	66.6	NR	66.7	NR
Gouda 2006[59]	CTX → CTX + RT	NR	NR	NR	NR	NR	NR	55	NR	40	NR	75	NR
	CTX + RT	NR	NR	NR	NR	NR	NR	65	NR	45	NR	79	NR
Belderbos 2007[54]	CTX → RT	16.2	12.8 to 22.6	1.06 (074 to 1.52	10.8	9.0 to 15.0	0.79 (0.56 to 1.10)	69	58.7 to 79.3	33.6	23 to 44.2	69.7	58.1 to 79.8
	CTX + RT	16.5	11.3 to 24.3		8.5	6.4 to 10.9		55.9	45.0 to 66.9	38.5	27.6 to 49.4	60.8	47.8 to 72.4
Vokes 2007[48]	CTX + RT	12	10 to 16	NR	7.0	NR	NR	NR	NR	29	NR	67	60 to 74
	CTX → CTX + RT	14	11 to 16	NR	8.0	NR	NR	NR	NR	31	NR	61	59 to 69
Liu 2008[53]	Low-dose weekly CTX (DOC) + RT (3D conformal) → CTX (DOC + CIS)	20	NR	NR	NR	NR	NR	69.8	NR	48.1	NR	81.8	NR
	Systemic CTX + RT (3D conformal) → CTX (DOC + CIS)	16	NR	NR	NR	NR	NR	66.5	NR	40.2	NR	86.4	NR
Socinski 2008a[55]	CTX → CTX (PAX + CARB) + RT	24.3	12.3 to 36.4	NR	14.9	7.9 to 24.3	NR	66.7	50.3 to 78.7	NR	NR	66.6	50.5 to 80.4
	CTX → CTX (GEM + CARB) + RT	12.5	9.4 to 27.6	NR	7.7	5.1 to 11.0	NR	50	29.9 to 67.2	NR	NR	69.2	48.2 to 85.7
Berghmans 2009[45]	CTX + RT → CTX	17.0	9.3 to 24.6	NR	7.3[a]	5.0 to 9.6	NR	NR	NR	NR	NR	57	36 to 78
	CTX → CTX + RT	23.9	13.3 to 34.5	NR	13.3[a]	8.7 to 17.6	NR	NR	NR	NR	NR	79	64 to 94

continued

TABLE 9 Trial outcomes (*continued*)

Reference ID	Treatment	Median OS			Median PFS			Survival 1 year		Survival 2 years		Tumour ORR	
		Months	95% CI	HR (95% CI)	Months	95% CI	HR (95% CI)	%	95% CI	%	95% CI	%	95% CI
Crvenkova 2009[57]	CTX → RT	13	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CTX + RT → CTX	22	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nyman 2009[58]	CTX → CTX + accelerated RT	17.69	11.15 to 36.25	NR	8.75	7.4 to 15.16	NR	64	NR	41	NR	33	NR
	CTX → CTX daily + conventional RT	17.68	11.97 to NR	NR	10.27	8.31 to 14.3	NR	62	NR	39	NR	70	NR
	CTX → CTX weekly + conventional RT	20.63	12.72 to 25.09	NR	9.31	7.33 to 13.78	NR	62	NR	38	NR	45	NR
Zhu 2009[60]	CTX + RT (3D conformal)	19.7	NR	NR	NR	NR	NR	70.5	NR	47.7	NR	68	NR
	CTX → RT (3D conformal)	18.2	NR	NR	NR	NR	NR	66.7	NR	42.9	NR	62	NR
Movsas 2010[61]	CTX + RT → CTX (GEM)	16.1	9.8 to 34.0	NR	5.4	2.7 to 7.9	NR	65.6	46.9 to 79.3	40.6	23.8 to 56.8	NR	NR
	CTX + RT → CTX (GEM + DOC)	29.5	16.4 to 52.0	NR	13.4	4.6 to 23.3	NR	71.9	52.9 to 84.3	55.7	36.8 to 70.9	NR	NR

CIS, cisplatin; HFX, hyperfractionated; NR, not reported.

a TTP not PFS.

Overall survival data available for inclusion in meta-analyses

Sequential chemoradiation compared with concurrent chemoradiation ($n = 4$)

Four trials[46,51,54,60] compared sequential CTX-RT with concurrent CTX-RT. The HRs for OS for two trials[51,54] were extracted directly from the published trial papers. Two studies[46,60] were excluded from the meta-analysis on OS because data were unavailable and it was impossible for the Assessment Group to estimate the OS HRs based on the published summary statistics. The trial by Zatloukal *et al.*[51] demonstrated significantly longer OS with concurrent CTX-RT (median survival 16.6 months) than with sequential CTX-RT (median survival 12.9 months) ($p = 0.023$, log-rank test; HR 0.61; 95% CI 0.39 to 0.93). The results from the trial described by Belderbos *et al.*[54] were not statistically significant. The pooled results from the OS meta-analysis comparing concurrent CTX-RT with sequential CTX-RT were therefore based on two trials. The results of this analysis are presented in *Figure 3* and appear to show an OS advantage for concurrent CTX-RT arms over sequential arms; this result is not statistically significant (HR 0.79; 95% CI 0.50 to 1.25). Visual examination of the forest plot indicates a non-statistically significant chi-squared test for heterogeneity ($p = 0.096$) and an I^2 statistic of 63.9%; the results suggest inconsistency in the direct evidence from the two trials.[51,54]

Sequential chemoradiation compared with concurrent/consolidation chemoradiation ($n = 4$)

Four trials[49,52,56,57] compared sequential CTX-RT with concurrent/consolidation CTX-RT. Concurrent/consolidation CTX-RT significantly increased median OS in a trial by Crvenkova *et al.*[57] Three trials[49,52,56] showed non-significant trends in favour of concurrent/consolidation CTX-RT compared with sequential CTX-RT.

One[52] of the four studies was excluded from the meta-analysis on OS because data were unavailable and it was impossible for the Assessment Group to estimate the OS HRs based on the published summary statistics. The OS HRs for one trial[49] were extracted directly from the published trial paper, while HRs for two trials[56,57] were estimated using summary statistics based on the methods described in the methods section of this report. The pooled results from the meta-analysis on OS comparing sequential CTX-RT with concurrent/consolidation CTX-RT were therefore based on data from three trials. The results of this analysis are presented in *Figure 4* and appear to show a statistically significant OS advantage for concurrent/consolidation CTX-RT treatment over sequential treatment; this result is statistically significant (HR 0.68; 95% CI 0.55 to 0.83). Visual examinations of the forest plot, the chi-squared test for heterogeneity ($p = 0.713$) and the I^2 statistic (0%) all suggest very good consistency.

Sequential chemoradiation compared with concurrent chemoradiation with or without consolidation ($n = 8$)

Eight trials[46,49,51,52,54,56,57,60] compared sequential CTX-RT with concurrent CTX-RT with or without consolidation and were considered for inclusion in the meta-analysis on OS. The HRs for OS for three trials[49,51,54] were extracted directly from the published trial papers, while HRs for two trials[56,57] were estimated using summary statistics based on the methods described in the methods section of this report. Three studies[47,52,61] were excluded from the meta-analysis on OS because data were unavailable and it was impossible for the Assessment Group to estimate the OS HRs based on the published summary statistics. Three trials[49,51,57] demonstrated significantly longer OS with concurrent CTX-RT with or without consolidation (median survival ranged from 16.3 to 22 months) than with sequential CTX-RT (median survival ranged from 12.9 to 14.5 months). The pooled results from the meta-analysis on OS comparing sequential CTX-RT with concurrent CTX-RT with or without consolidation were based on data from five trials. The results of this analysis are presented in *Figure 5* and appear to show a statistically significant OS advantage for concurrent CTX-RT with or without consolidation over sequential treatment; this result is statistically significant (HR 0.72; 95% CI 0.61 to 0.84). Visual examinations of the forest plot, the chi-squared test for heterogeneity ($p = 0.445$) and the I^2 statistic (0%) all suggest very good consistency.

Overall survival data unavailable for inclusion in direct meta-analysis

Induction/concurrent chemoradiation compared with concurrent chemoradiation ($n = 3$)

Three trials[48,50,59] compared induction/concurrent CTX-RT with concurrent CTX-RT. None of the studies presented OS HRs and therefore no meta-analysis was undertaken because it was impossible for the Assessment Group to estimate the OS HRs based on the published summary statistics. As shown in *Table 10* the induction CTX used in two of the three trials was the same (PAX plus CARB). Direct results from each of the three studies indicated that the addition of induction CTX increased toxicity and provided no survival benefit over concurrent CTX-RT alone.

Induction/concurrent chemoradiation compared with concurrent/consolidation chemoradiation ($n = 2$)

Two trials[45,52] comparing induction/concurrent CTX-RT with concurrent/consolidation CTX-RT were considered for inclusion in the meta-analysis on OS. The studies did not present OS HRs and therefore no meta-analysis was undertaken because it was impossible for the Assessment Group to estimate the OS HRs based on the published summary statistics. It is noted that the induction and consolidation chemotherapies used in the trials were different (see *Table 10*). Results from both trials demonstrate a longer median survival time with concurrent/consolidation CTX-RT than with induction/concurrent CTX-RT (16.3 months vs 12.7 months; 23.9 months vs 17 months); these results were not statistically significantly different.

Induction/concurrent chemoradiation compared with induction/concurrent chemoradiation ($n = 3$)

Three trials[47,55,58] that compared induction/concurrent CTX-RT with induction/concurrent CTX-RT were considered for inclusion in the meta-analysis on OS. None of the studies presented OS HRs data and therefore no meta-analysis was undertaken because it was impossible for the Assessment Group to estimate the OS HRs based on the published summary statistics. The three trials were very different to each other as is shown in *Table 10*. In the trial by Nyman *et al.*,[58] all patients had the same induction CTX following randomisation into three arms. Concurrent weekly CTX with conventional RT was associated with a longer median survival (20.63 months) than concurrent CTX-RT with accelerated RT (17.69 months) and concurrent daily CTX with conventional RT (17.68 months).

The trial by Vokes *et al.*[47] compared induction CTX using GEM, VNB or PAX in combination with cisplatin (CIS) in addition to concurrent CTX-RT; median survival for all patients was 17 months (range 14.8–18.3 months). The trial by Socinski *et al.*[55] evaluated induction CTX with either PAX plus CARB or GEM plus CARB. On day 43, the PAX plus CARB arm received weekly CARB plus PAX whereas the GEM plus CARB arm received biweekly GEM. Both arms received CTX concurrently with 74 Gy of thoracic RT utilising three-dimensional treatment planning. The median survival time was 24.3 months in the PAX plus CARB arm compared with 12.5 months in the GEM plus CARB arm. The GEM plus CARB arm was closed prematurely because of a high rate of grade 4/5 pulmonary toxicity.

Concurrent chemoradiation compared with concurrent chemoradiation ($n = 2$)

Two trials[62,63] comparing concurrent CTX-RT with concurrent CRX-RT were considered for inclusion in the meta-analysis on OS. None of the studies presented OS HRs data and therefore no meta-analysis was undertaken because it was impossible for the Assessment Group to estimate the OS HRs based on the published summary statistics. The trial by Jeremic *et al.*[63] aimed to investigate whether or not it is advantageous to add weekend CTX consisting of ETOP plus CARB to hyperfractionated RT and concurrent daily ETOP plus CARB. No difference was found regarding median survival time or 5-year survival rates (20 vs 22 months; 20% vs 23%; $p = 0.57$). The trial by Schild *et al.*[62] demonstrated no statistically significant difference in OS between ETOP plus CIS plus RT once daily and ETOP plus CIS plus RT twice daily (14 vs 15 months).

TABLE 10 Summary of CTX-RT combinations for each included trial by treatment option

Reference ID	Concurrent CTX-RT	Sequential CTX-RT	Induction/concurrent CTX-RT	Concurrent/consolidation CTX-RT
Jeremic 2001[63]	ETOP + CARB + HFXRT vs ETOP + CARB + HFXRT			
Komaki 2002[50]	ETOP + CIS + HFXRT		VBL + CIS → CIS + RT	
Schild 2002[62]	ETOP + CIS + RT vs ETOP + CIS + HFXRT			
Vokes 2002[47]			GEM + CIS → GEM + CIS + RT vs PAX + CIS → PAX + CIS + RT vs VNB + CIS → VNB + CIS + RT	
Zatloukal 2004[51]	VNB + CIS + RT	VNB + CIS → RT		
Belani 2005[52]		PAX + CARB → RT	PAX + CARB → PAX + CARB + RT	PAX + RT → CARB
Fournel 2005[49]		VNB + CIS → RT		ETOP + CIS + RT → VNB + CIS
Reinfuss 2005[46]	VNB + CIS + RT	VNB + CIS → RT		
Dasgupta 2006[56]		ETOP + CIS → RT + ETOP + CIS		ETOP + CIS + RT → ETOP + CIS
Gouda 2006[59]	PAX + CARB + RT		PAX + CARB → PAX + CARB + RT	
Belderbos 2007[54]	CIS + RT	GEM + CIS → RT		
Vokes 2007[48]	PAX + CARB + RT		PAX + CARB → PAX + CARB + RT	
Liu 2008[53]				DOC + CIS + RT → DOC + CIS vs DOC + RT → DOC + CIS
Socinski 2008a[55]			GEM + CARB → GEM + RT vs PAX + CARB → PAX + CARB + RT	
Berghmans 2009[45]			GEM + VNB + CIS → GEM + VNB + CIS + RT	GEM + VNB + CIS + RT → GEM + VNB + CIS
Crvenkova 2009[57]		ETOP + CARB → RT		ETOP + CIS + RT → ETOP + CARB
Nyman 2009[58]			PAX + CARB → PAX + RT vs PAX + CARB → PAX + RT vs PAX + CARB → PAX + CARB + RT	
Zhu 2009[60]	VNB + CIS + RT	VNB + CIS → RT		
Movsas 2010[61]				ETOP + CIS + RT → GEM vs ETOP + CIS + RT → GEM + DOC

HFXRT, hyperfractionated RT; VBL, vinblastine.

Studies	Sequential/concurrent	Sequential/concurrent patients	Hazard ratios (95% CI)	Median OS (months)
Zatloukal 2004[52]	VBN + CIS- > RT/VBN + CIS + RT	50/52	0.61 (0.40 to 0.94)	12.9/16.6
Belderbos 2007[55]	GEM + CIS- > RT/CIS + RT	78/80	0.98 (0.69 to 1.39)	16.2/16.5
Overall (I^2 = 63.9%, p = 0.096)			0.79 (0.50 to 1.25)	

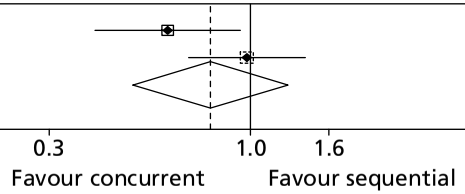

FIGURE 3 Summary of the direct evidence results for OS for trials comparing sequential CTX-RT with concurrent CTX-RT.

Studies	Sequential/concurrent and consoldidation	Sequential/concurrent and consolidation patients	Hazard ratios (95% CI)	Median OS (months)
Fournel 2005[50]	VNB + CIS- > RT/ETOP + CIS + RT- > VNB + CIS	101/100	0.67 (0.52 to 0.86)	14.5/16.3
Dasgupta 2006[57]	ETOP + CIS- > RT/ETOP + CIS + RT- > ETOP + CIS	35/36	0.84 (0.47 to 1.52)	NR/NR
Crvenkova 2009[58]	ETOP + CARB- > RT/ETOP + CIS + RT- > ETOP + CARB	45/40	0.62 (0.39 to 0.98)	13/22
Overall (I^2 = 0.0%, p = 0.713)			0.68 (0.55 to 0.83)	

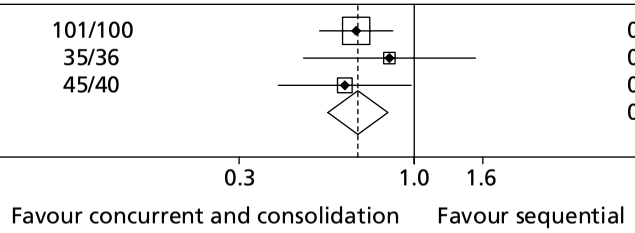

FIGURE 4 Summary of the direct evidence results for OS for trials comparing sequential CTX-RT with concurrent/consolidation CTX-RT. NR, not reported.

Studies	Sequential/concurrent	Sequential/concurrent patients	Hazard ratios (95% CI)	Median OS (months)
Zatloukal 2004[52]	VNB + CIS- > RT/VNB + CIS + RT	50/52	0.61 (0.40 to 0.94)	12.9/16.6
Fournel 2005[50]	VNB + CIS- > RT/ETOP + CIS + RT- > VNB + CIS	101/100	0.67 (0.52 to 0.86)	14.5/16.3
Belderbos 2007[55]	Gem + CIS- > RT/ CIS + RT	78/80	0.94 (0.66 to 1.35)	16.2/16.5
Dasgupta 2006[57]	ETOP + CIS- > RT/ETOP + CIS + RT- > ETOP + CIS	35/36	0.84 (0.47 to 1.52)	NR/NR
Crvenkova 2009[58]	ETOP + CARB- > RT/ETOP + CIS + RT- > ETOP + CARB	45/40	0.62 (0.39 to 0.98)	13/22
Overall (I^2 = 0.0%, p = 0.445)			0.72 (0.61 to 0.84)	

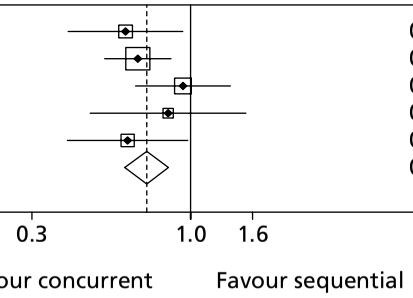

FIGURE 5 Summary of the direct evidence results for OS for trials comparing sequential CTX-RT with concurrent CTX-RT with or without consolidation. NR, not reported

Concurrent/consolidation chemoradiation compared with concurrent/consolidation chemoradiation ($n = 2$)

Two trials[53,61] comparing concurrent/consolidation CTX-RT with concurrent/consolidation CTX-RT were considered for inclusion in the meta-analysis on OS. None of the studies presented OS HRs and therefore no meta-analysis was undertaken because it was impossible for the Assessment Group to estimate the OS HRs based on the published summary statistics. The two trials were very different to each other as shown in *Table 10*. The trial by Movsas *et al.*[61] compared two different consolidation CTX interventions (GEM compared with GEM plus DOC). Patients were randomised after they had all received the same concurrent CTX-RT. Consolidation therapy with GEM was associated with a median OS of 16.1 months compared with 29.5 months for GEM plus DOC. The trial by Liu *et al.*[53] showed no significant difference in 1- and 2-year survival rates between low-dose weekly DOC and standard DOC plus CIS – both groups received concurrent RT and the same consolidation CTX-RT. Median survival time was 20 months for the low-dose weekly DOC group and 16 months for the standard DOC plus CIS group.

Adverse events

Adverse events are presented in *Appendix 11*. Concurrent CTX-RT is associated with higher oesophageal toxicity than sequential CTX-RT. In the trial by Belani *et al.*[52] the most common locoregional grade 3/4 toxicity during and after thoracic RT was oesophagitis, which was more pronounced with concurrent CTX-RT than sequential CTX-RT. In the trial by Belderbos *et al.*[54] oesophagitis grade 3/4 was more frequent in the induction/concurrent CTX-RT arm than in the sequential CTX-RT arm (14% vs 5%); however, late oesophagitis grade 3 was 4% in both arms. Pneumonitis grade 3/4 was 14% in the sequential CTX-RT and 18% in the concurrent CTX-RT arm. In the trial by Crvenkova and Krstevska,[57] acute oesophagitis and incidence of neutropenia were higher in the concurrent/consolidation CTX-RT arm than in the sequential CTX-RT arm; grade 3 oesophagitis was characteristic only of concurrent CTX-RT and was a reason for RT interruption (no longer than 7 days). In the trial by Fournel *et al.*,[49] oesophageal toxicity was significantly more frequent in the concurrent/consolidation CTX-RT arm than in the sequential CTX-RT arm (32% vs 3%). Treatment had to be stopped because of acute severe toxicity in 18% of patients in the sequential CTX-RT arm and 23% of patients in the concurrent/consolidation CTX-RT arm.

In the Komaki *et al.*[50] trial ,the incidence of acute oesophagitis was significantly higher among patients in the concurrent hyperfractionated RT group than among those in the induction/concurrent standard RT group ($p < 0.0001$). Analysis of late toxicity showed that chronic oesophageal toxicity was significantly more frequent in the concurrent hyperfractionated RT group than in the induction/concurrent standard RT group ($p = 0.003$). In addition, the incidence of acute haematological toxicity was significantly higher among patients treated with induction/concurrent standard RT ($p = 0.01$ for anaemia and $p = 0.03$ for other haematological toxicities) than among those treated with concurrent hyperfractionated RT.

In the Reinfuss *et al.* trial,[46] the rate of toxicity in the concurrent CTX-RT arm was statistically significantly higher than the rate in the sequential arm. Full treatment according to the plan was given to 96.7% of patients treated sequentially and to 75% in the concurrently treated group. In 6.8% of patients undergoing sequential treatment and 14.3% of patients undergoing concurrent treatment, toxicity enforced breaks in irradiation, lasting 8–10 days, after which treatment was resumed and completed.

In the trial by Belderbos *et al.*,[54] acute haematological toxicity grade 3/4 was more pronounced in the sequential arm than in the concurrent arm (30% vs 6%). In the trial reported by Berghman *et al.*,[45] there was no difference in toxicity, except for more leucopenia and infection in the concurrent/consolidation CTX-RT arm than in the induction/concurrent CTX-RT arm. Secondary anaemia was more frequent in the sequential treatment group than in the concurrent arm in Crvenkova *et al*.[57] In the trial by Fournel *et al.*,[49] the incidence of neutropenia, including grade 4 neutropenia, was higher with sequential CTX-RT than with concurrent CTX-RT ($p = 0.008$). In addition, peripheral neuropathies were also more frequent in the sequential CTX-RT arm than in the concurrent arm.

In the trial by Jeremic *et al.*,[63] patients treated with the addition of weekend CTX had significantly more high-grade (> grade 3) haematological toxicity, including leucopenia, thrombocytopenia and anaemia ($p = 0.0046$). Late high-grade toxicity was not different between the two treatment groups.

Movsas *et al.*[61] reported that grade 3 or 4 events, including neutropenia (9/32 or 28.1% vs 18/32 or 56.3%; $p = 0.03$), anaemia (1/32 or 3.1% vs 6/32 or 18.8%; $p = 0.05$) and fatigue (2/32 or 6.3% vs 5/32 or 15.6%; not significant), were more frequent with consolidation GEM plus DOC than with consolidation GEM alone.

In the trial by Liu *et al.*[53] patients with grade 3/4 toxicity accounted for 14.3% of patients in the low-dose weekly DOC alone group and 28.6% of patients in the standard DOC plus CIS group ($\chi^2 = 0.765$, $p = 0.382$; $\chi^2 = 1.108$, $p = 0.292$, respectively). There were no statistically significant differences in toxicity except for nausea/vomiting, which was significantly higher in the standard DOC plus CIS group for grades 3/4.

Quality of life

Only one trial[58] reported on HRQoL and the authors plan to report the results in full in a separate publication. Preliminary analyses showed no statistically significant differences between the trial arms for expected toxicity, dyspnoea, dysphagia and global HRQoL.

Summary of results

Nineteen RCTs met the inclusion criteria and compared CTX-RT with CTX-RT. The majority of patients were male and middle-aged and had disease stage III with adenocarcinoma or squamous cell carcinoma and a PS of 0–1.

Overall, the methodological quality of included trials was poor with nearly all trials failing to report relevant methodology; in particular, methods of randomisation and allocation concealment were reported inadequately. Six trials reported some imbalance between trial groups at baseline, of which two trials reported a statistically significant imbalance between treatment groups for baseline disease stage. None of the trials was reported as being blinded. Seven trials assessed all participants according to the groups to which they were randomised. Only one trial reported any HRQoL data and preliminary analysis showed no statistically significant differences between the arms according to expected toxicity, dyspnoea, dysphagia and global HRQoL.

Five trials were closed prematurely mainly because of poor accrual, and in one trial the GEM plus CARB arm was closed prematurely because of a high rate of grade 4/5 pulmonary toxicity. Only three trials had international centres and only six were clearly Phase III trials. Sources of funding were a mixture of pharmaceutical and research grants; seven trials failed to report the source of funding. Only five trials were powered sufficiently to evaluate the primary outcome of the trial, of which two trials were powered to detect differences between treatment groups in 2-year survival rate.

Twelve trials compared various regimens of sequential, concurrent and consolidation CTX-RT. Five trials compared different types of RT or CTX, one trial compared RT once daily with RT twice daily and another trial assessed the addition of weekend CTX. In addition, there were different CTX agents and different radiation doses both across and within trials, and number of fractions, schedule, intensity and overall treatment time also varied between trials.

Across the trials, median OS ranged from 12 to 29.5 months and survival rate ranged from 37% to 80% at 1 year and from 14.3% to 66.6% at 2 years. Median PFS ranged from 5.4 to 14.9 months and median TTP ranged from 7.3 to 13.3 months. Tumour ORR ranged from 33% to 88%.

Results of individual studies showed that concurrent CTX-RT is associated with significantly longer survival than sequential CTX-RT[51,57] and that concurrent/consolidation CTX-RT is associated with significantly longer survival than induction/concurrent CTX-RT.[45,52]

The Assessment Group performed several direct evidence comparisons (meta-analysis) using data combining induction, sequential, concurrent and consolidation CTX-RT. The results appear to show no statistically significant evidence to support OS advantage for concurrent CTX-RT arms over sequential CTX-RT arms. However, when concurrent/consolidation treatments were compared with sequential treatments, the difference in OS was shown to be statistically significant. When sequential CTX-RT was compared with concurrent CTX-RT with or without consolidation, the latter yielded a statistically significant improvement in OS.

Only 12 trials reported information about CTX and RT treatment received in terms of RDI. In the trials comparing sequential CTX-RT with concurrent CTX-RT, more patients in the concurrent arms tolerated higher doses of RT. Concurrent/consolidation CTX-RT may be easier to tolerate than induction/concurrent CTX-RT. However, concurrent CTX-RT is associated with greater oesophagus toxicity than sequential CTX-RT.

The Assessment Group concluded that the 19 trials included in the systematic review were too disparate to form any conclusion as to the effectiveness of individual CTX agents or types of RT.

Chapter 4 Discussion

Chemoradiation treatment is common practice for stage III cancers for those patients whom clinicians believe may be curable. This review was carried out as part of a larger project[32] looking at first-line treatments for patients with locally advanced and/or metastatic lung cancer. It was the opinion of the members of the clinical panel for the project that patients with stage IIIA or IIIB potentially curable disease are different from those who are considered for only palliative treatment of more advanced disease. The clinical panel was of the opinion that the review of CTX-RT treatments for patients with potentially curable disease should be reported separately.

There have been previous reviews that looked at this question.[22,35,64] However, given the advances in treatment, in the areas of both CTX and RT, it was felt worthwhile to examine the question again and to limit the dates of included trials to represent current, rather than historical, clinical practice.

Principal findings

The quality of the studies included in this review is generally poor and there are significant differences in the patient populations and treatments (both RT and CTX) within and across the studies, limiting the conclusions that can be drawn. The results of a series of meta-analyses conducted by the Assessment Group appear to demonstrate a statistically significantly improved OS with the use of concurrent/consolidation CTX-RT over sequential CTX-RT and statistically significantly improved OS with the use of concurrent CTX-RT (with or without consolidation) over sequential treatment. The Assessment Group did not find a statistically significant difference in OS between concurrent CTX-RT and sequential CTX-RT although there appears to be a trend towards an OS advantage for patients receiving concurrent CTX-RT. It is noted that concurrent CTX-RT is associated with significant oesophageal toxicity.

It should be acknowledged, however, that both the RT and CTX aspects of care for patients with NSCLC have changed significantly over the past 10 years and can be expected to continue to evolve, thus limiting the value of any comparison of treatments over time. This includes changes in methods of diagnosis and categorisation of the disease. In addition, ETOP appears to be commonly used in the UK but is not licensed for use in lung cancer.

Strengths and limitations

This report provides a summary and critical appraisal of a comprehensive evidence base of CTX-RT trials. It may be that additional trials have been reported since our last literature search but it is unlikely that their results, unless from very large, well-designed trials, would change the conclusions of the review.

Although CTX-RT is an established treatment regimen for eligible patients, how best to combine CTX and RT remains unclear. The optimal type and dose of CTX and RT also remain unclear. The updated NICE guidelines[5] on the diagnosis and treatment of lung cancer recommend further research into the incorporation of accelerated RT fractionations within CTX treatment regimens and research into combinations of new targeted agents [e.g. epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitors] and RT regimens. This highlights the uncertainty regarding best first-line treatment options for patients with NSCLC. Unfortunately the quality and the heterogeneity of the available data mean that this review has not been able to provide clear direction for clinicians regarding these important issues.

It is also disappointing that the quality of the research in this area does not meet the accepted quality standards regarding trial design and reporting. Quality assessment of included trials by the Assessment

Group demonstrated that the included studies were generally of poor quality except for the criterion of patient follow-up. It could be argued that it is not possible to blind patients and care providers or that it is difficult to recruit enough patients to allow for trials with a sufficient size for conclusions to be drawn. However, there is no reason why concealment of allocation and appropriate randomisation cannot be achieved. The lack of balance across the arms in a number of trials indicates that randomisation procedures did not in fact provide equivalent groups in a number of instances.

In addition, there is no reason why outcome measures with appropriate statistical analysis cannot be presented (e.g. CIs around data points such as OS). This selective and incomplete reporting of outcomes in the included trials severely limited data synthesis. It is difficult to understand how authors of research reports can state that they have measured outcomes such as OS and then fail to report their data comprehensibly.

Despite its importance and relevance to patients and clinicians, there are few reports of HRQoL in the NSCLC trials. It is acknowledged that collecting and reporting HRQoL data in RCTs may be difficult. However, such data are critically important if the appropriate analyses are to be carried out to inform health policy decisions. Measuring HRQoL outcomes in patients with advanced NSCLC is reported to be particularly difficult because of the severity of symptoms, the side effects of CTX-RT treatment and early deaths associated with the disease. However, it is estimated that about half of all patients with advanced NSCLC could reasonably be expected to complete HRQoL instruments within a clinical trial setting (Paul Beckett, Consultant Physician for Burton Hospital NHS Trust, 2011, personal communication).

It is acknowledged that, even when HRQoL data are available, comparison across trials is complex. This is due to an array of factors including the number and timing of HRQoL measurements available and administered to patients; the intercountry cultural differences in how HRQoL is interpreted; and the resource requirements for its collection (patient explanations and assistance in completing questionnaires).

Uncertainties

As noted above, there have been recent changes in the diagnostic criteria used for lung cancer. There are differences between UICC version 6 and version 7 that are relevant to advanced lung disease; for example, pleural effusion is classed as stage IIIB in version 6 and has been moved to stage IV in version 7. Most of the trials included in the Assessment Group's systematic review will have used version 6, and so it should be noted that many of the patients classified as stage IIIB within the included trials would now be classified as stage IV and it is unclear what their treatment options would have been. This stage migration needs to be accounted for in future reviews when comparing outcomes across trials using different TNM classifications.

It is unknown what effect variance in exposure to treatment may have on clinical efficacy and safety outcomes. For example, it may be that the survival benefit associated with concurrent/consolidation CTX-RT could be accounted for by the significantly fewer patients in the sequential CTX-RT arms receiving a full course of RT rather than by concurrent CTX-RT increasing radiosensitisation (and therefore the effect of RT). More research in this area is warranted.

Other relevant factors

As noted earlier, there have been significant changes to the delivery of care for NSCLC patients. Over the past 10 years there has been a plethora of new CTX treatments approved for use including those that have been shown to be more effective in different disease categories [e.g. pemetrexed (Alimta®, Eli Lilly) for patients with non-squamous disease and gefitinib (Iressa®, AstraZeneca) for patients with EGFR mutation-positive tumours]. This requires changes in the diagnostic and treatment paths taken by patients as it is

expected that in the near future all patients will have appropriate histological and genetic testing carried out. This will provide more information for clinicians to aid in planning patient care but will obviously make treatment choices more complex (Brown T, Pilkington G, Bagust A, Boland A, Oyee J, Tudur-Smith C, *et al*. Clinical and cost effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation. *Health Technol Assess*, in preparation).

As noted above, these changes in diagnosis and treatment have been compounded by changes in the staging of NSCLC and these changes mean that comparison of results from past and future studies will be difficult and perhaps not possible.

Chapter 5 Conclusion

This review identified that the research conducted in the area of CTX-RT was generally of poor quality and suffered from a lack of reporting of all important clinical findings, including OS. In addition, there are within- and between-trial variations in treatment protocols including treatment duration, sequencing and length, RT exposure and type of CTX. These wide variations severely limited the combination of trial results.

Meta-analyses conducted as part of this review demonstrated a small but statistically significant improvement in OS in patients receiving concurrent/consolidation CTX-RT compared with sequential CTX-RT and statistically significantly improved OS with the use of concurrent CTX-RT (with or without consolidation) over sequential treatment. However, as noted, the variation in treatment protocols and the changes in the diagnostic criteria and staging used in NSCLC mean that the results of comparisons across these trials and with future trials need to be viewed with caution.

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Angela Boland	Input into all aspects of the clinical component of the review.
Tamara Brown	Project management, data management, systematic review of clinical effectiveness data and preparation of report.
Rumona Dickson	Input into all aspects of the clinical component of the review.
Yenal Dundar	Development of search strategies.
Gerlinde Pilkington	Data extraction and quality assessment of the clinical trials.
James Oyee	Assessment of statistics and data analysis including meta-analyses.
Elizabeth Richards	Data extraction of clinical trials.
Catrin Tudur Smith	Statistical expertise.
Rongrong Yang	Data extraction of clinical trials.

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Appendix 1 Details of clinical search strategies

Ovid MEDLINE(R) 1990 to March Week 3 2009

		Results
1	randomized controlled trial.pt.	266,601
2	controlled clinical trial.pt.	78,726
3	randomized.ab.	177,144
4	placebo.ab.	110,573
5	randomly.ab.	128,581
6	trial.ab.	184,266
7	or/1–6	579,686
8	(animals not (humans and animals)).sh.	3,254,838
9	7 not 8	525,513
10	exp Carcinoma, Non-Small-Cell Lung/ or nsclc.ti,ab.	18,909
11	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.	18,385
12	10 or 11	22,812
13	exp Antineoplastic Combined Chemotherapy Protocols/ or *Combined Modality Therapy/ or exp chemotherapy, adjuvant/ or exp Radiotherapy/	182,017
14	(chemotherap$ or radiotherap$ or chemo-radiation or chemoradiation or support$ care$ or palliat$ care$).ti,ab.	254,221
15	(vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab).ab.	20,673
16	or/13–15	355,832
17	9 and 12 and 16	3045
18	limit 17 to (english language and yr="1990 – 2009")	2594

EMBASE 1990 to 2009 Week 13

		Results
1	Randomized Controlled Trial/	167,319
2	randomized.ab.	171,365
3	placebo.ab.	106,176
4	randomly.ab.	114,323
5	trial.ab.	168,003
6	controlled clinical trial.pt.	0
7	Controlled Clinical Trial/	58,798
8	or/1–7	464,615
9	limit 8 to human	396,769
10	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.	18,740
11	exp Lung non Small Cell Cancer/ or nsclc.ti,ab.	22,601
12	10 or 11	25,216
13	Vindesine/ or Docetaxel/ or Cisplatin/ or Etoposide/ or Paclitaxel/ or Carboplatin/ or Navelbine/	128,596
14	(chemotherap$ or radiotherap$ or chemo-radiation or chemoradiation or support$ care$ or palliat$ care$).ti,ab.	220,301
15	(vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab).ab.	20,371
16	exp Cancer Radiotherapy/ or exp Chemotherapy/	225,579
17	or/13–16	386,860
18	9 and 12 and 17	3521
19	limit 18 to (english language and yr="1990 – 2009")	3034

The Cochrane Library (Issue 3 of 4, July 2010)

"non small cell lung cancer in Title, Abstract or Keywords and (vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab or vindesine or docetaxel or cisplatin or etoposide or paclitaxel or carboplatin or navelbine) in Title, Abstract or Keywords in Cochrane Methodology Register"

Appendix 2 Details of clinical data abstraction

Study details

- Author/year/EndNote reference.
- Randomisation.
- Recruitment.
- Funding.
- Country.
- Power.
- Setting.
- Population.
- Inclusion/exclusion criteria (summary of trial inclusion/exclusion criteria).
- ITT analysis.
- Length of follow-up.

Intervention details

- Intervention [i.e. drug name(s) and details].
- Dose of intervention.
- Duration of intervention.

Participant characteristics

- Number of participants randomised.
- Number of participants assessed for primary outcome.
- Age.
- Sex.
- PS.
- Disease stage.
- Whether or not baseline demographics and disease state were comparable.

Outcomes

- OS.
- Median survival time.
- Survival rate.
- PFS.
- Tumour response rate.
- Quality of life.
- Haematological toxicity.
- Non-haematological toxicity.
- Toxic death.

Appendix 3 Details of clinical trial quality assessment

The quality of RCTs is assessed using the following criteria outlined in CRD's *Guidance for Undertaking Reviews in Health Care*:[34]

- Was the method used to assign participants to the treatment groups really random? (Computer-generated random numbers and random number tables will be accepted as adequate; inadequate approaches will include the use of alternation, case record numbers, birth dates and days of the week.)
- Was the allocation of treatment concealed? (Concealment will be deemed adequate when randomisation is centralised or pharmacy controlled or when the following are used: serially numbered identical containers, on-site computer-based systems in which the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes, even if opaque.)
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and PS?
- Was baseline comparability achieved in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and PS?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
- Were the reasons for withdrawals stated?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Was an ITT analysis included?

Items are graded in terms of ✓✗ (item properly addressed), ✗ (item not properly addressed), ✓✗ (item partially addressed), NS (unclear or not enough information) or NA (not applicable).

Appendix 4 Code from the Multi-parameter Evidence Synthesis Research Group

```
model{
#Model for log-hazard ratios
for(i in 1:ndp){
        prec[i]<- 1/(se[i]*se[i])
        lhr[i]~dnorm(delta[i],prec[i])

#Random effects model for log hazard ratios
                delta[i] ~ dnorm(md[i],taud[i])
                taud[i] <- tau * (1 + equals(arm[i],3) /3)
                md[i] <- d[t[i]] - d[b[i]] + equals(arm[i],3) * sw[i]
#Calculation of residual deviance
        rhat[i] <- lhr[i] * prec[i]
        dev[i] <- (lhr[i] - delta[i])*(lhr[i] - delta[i])/(se[i]*se[i])
        }
        resdev <- sum(dev[])

# Adjustment for multi-arm trials
        sw[1]<- 0
        for (i in 2:ndp) { sw[i] <- (delta[i-1] - d[t[i-1]] + d[b[i-1]])/2}

#Non-informative priors for log hazard ratios
        d[1]<- 0
        for (k in 2:nt){
        d[k] ~ dnorm(0,.00001) # vague priors for basic parameters

        }

        sd~dunif(0,100)
        tau<-1/pow(sd,2)

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:nt){
        rk[k]<- rank(d[],k)

        best[k]<-equals(rk[k],1)
        }

#All pair-wise log hazard ratios and hazard ratios
for (c in 1:nt-1){
        for (k in (c+1):nt){
                lhzr[c,k] <- d[k] - d[c]
                HR[c,k] <- exp(lhzr[c,k])
                }
        }
}
```

Appendix 5 Excluded studies with reasons for exclusion

Reference	Reason for exclusion
Fisher 2000[65]	Short report to Negoro *et al.*[66]
Grigorescu 2002[67]	Quasi-randomised
Lin 2002[68]	Not a RCT
Georgoulias 2003[69]	Interim analysis (not complete patient sample) to Georgoulias *et al.*[70]
Leong 2003[71]	Amifostine (cytoprotective adjuvant used in cancer CTX and RT; indication for NSCLC withdrawn 2005)
Miller 2003[72]	Dosing study using sequentially enrolled cohorts
Semrau 2003[73]	No English abstract
Teng 2003[74a]	Not a RCT
Vansteenkiste 2003[75]	Detailed individual symptom control analysis and the influence of CIS use, age, PS and duration of treatment of Vansteenkiste *et al.*[76]
O'Brien 2004[77]	PLAT-based CTX with or without SRL172 (killed *Mycobacterium vaccae* suspension)
Gao 2005[78a]	Unclear if patients were CTX naive
Liu 2006[79a]	Unclear if patients were CTX naive
Ramalingam 2006[80]	Subanalysis by age of Belani *et al.*[81] (not randomised by age)
Xu 2006[82a]	Does not report survival (only response rates and AEs)
Gridelli 2007[83]	Rofecoxib (withdrawn)
Gridelli 2008[84]	No outcome data – rationale and protocol only
Zhang 2008[85a]	Unclear if patients were CTX naive

a Required translation – abstract English.

Appendix 6 Trial characteristics

Study ID	Aim	Phase	Funding	Multicentre	International	Country	Sufficiently powered	Follow-up, median (months)
Jeremic 2001[63]	To investigate whether or not the addition of weekend CTX consisting of CARB + ETOP to HFXRT and concurrent daily CARB + ETOP offers an advantage over the same HFXRT/daily CARB + ETOP	III	Grant-in-Aid for Scientific Research (B) from the Japanese Ministry of Education, Science and Culture	No	No	Yugoslavia	Yes	60
Komaki 2002[50]	To evaluate the toxicity and efficacy of induction CTX followed by once-daily RT and concurrent CTX and HFXRT	II	National Cancer Institute	Yes	No	USA	Unclear	NS
Schild 2002[62]	To compare CTX + RT twice daily or four times daily	III	Public Health Service Grants	Yes	No	USA	Yes	43
Vokes 2002[47]	To evaluate new drugs in combination with CIS in unresectable NSCLC stage III	II	National Cancer Institute	Yes	No	USA	Yes	43
Zatloukal 2004[51]	To compare the safety and efficacy of concurrent and sequential CTX-RT with CTX consisting of a CIS and VNB regimen, in patients with locally advanced NSCLC	NS	Ministry of Health of the Czech Republic	Yes	No	Czech Republic	No	39
Belani 2005[52]	To determine the optimal sequencing and integration of PAX + CARB with standard daily thoracic RT in patients with locally advanced unresected stage III NSCLC	II	Bristol-Myers Squibb	Yes	No	USA	Unclear	39.6
Fournel 2005[49]	To compare the survival impact of concurrent vs sequential treatment with RT and CTX in unresectable stage III NSCLC	III	Pierre Fabre Institute of Oncology, France	Yes	No	France	No	57.6
Reinfuss 2005[46]	To compare the results of sequential and concurrent CTX-RT	NS	NS	No	No	Poland	Unclear	29 (mean)
Dasgupta 2006[56]	To evaluate different combination regimens of RT and CTX in unresectable NSCLC	III	NS	No	No	India	Unclear	24 (mean)

Study ID	Aim	Phase	Funding	Multicentre	International	Country	Sufficiently powered	Follow-up, median (months)
Gouda 2006[59]	To evaluate the results of combination CARB + PAX concomitantly with RT and also the benefit of two cycles of induction CTX	NS	NS	Yes	No	Egypt	Unclear	24
Belderbos 2007[54]	To compare concurrent CTX-RT and sequential CTX-RT for inoperable NSCLC patients stages I–III	II	National Cancer Institute	Yes	Yes	Germany, Netherlands, France, Belgium	No	16.5
Vokes 2007[48]	To evaluate whether or not induction CTX before concurrent CTX-RT would result in improved survival	III	National Cancer Institute	Yes	No	USA	Yes	38
Liu 2008[53]	To evaluate the efficacy and toxicity of concurrent CTX-RT with low-dose weekly DOC followed by consolidation CTX with DOC + CIS in stage III NSCLC	NS	NS	No	No	China	Unclear	20
Socinski 2008[55]	To evaluate 74-Gy thoracic RT with induction and concurrent CTX in stage IIIA/B NSCLC	II	National Cancer Institute	Yes	No	USA	Unclear	42/49
Berghmans 2009[45]	To determine the best sequence and safety of CTX and CTX-RT, using a regimen CIS + GEM + VNB	III	NS	Yes	Yes	Belgium, France, Spain, Greece	No	NS
Crvenkova 2009[57]	To compare the survival impact of concurrent vs sequential treatment with RT and CTX in inoperable stage III NSCLC	NS	NS	No	No	Former Yugoslav Republic of Macedonia	Unclear	NS
Nyman 2009[58]	To improve locoregional control by testing accelerated RT or concurrent daily or weekly CTX with conventional RT	II	Bristol-Myers Squibb Scandinavia	Yes	No	Sweden	Yes	52
Zhu 2009[60]	To compare sequential vs concurrent CTX-RT for stage III NSCLC	NS	NS	No	No	China	Unclear	24
Movsas 2010[61]	To assess consolidation with either GEM alone or with DOC after CTX-RT	II	Lilly, USA	Yes	Yes	USA, China, Argentina, Republic of Korea	No	36

HFXRT, hyperfractionated RT; NS, not stated.

Appendix 7 Intervention details

Study ID	Arm 1	Arm 2	Arm 3
Jeremic 2001[63]	**Concurrent without weekend CTX** HFXRT to a total tumour dose of 69.6 Gy via 1.2 Gy b.i.d. fractionation and daily 50 mg each of CARB + ETOP during the RT course (Mondays to Fridays). Weekly dose CARB 250 mg	**Concurrent with weekend CTX** Same HFXRT as arm 1 with daily 30 mg each of CARB + ETOP (Mondays to Fridays), with weekend (Saturdays and Sundays) 100 mg each of CARB + ETOP during the RT course. Weekly dose CARB 350 mg	
Komaki 2002[50]	**Induction/concurrent (standard RT)** Induction CTX (VBL 5 mg/m^2 i.v. bolus weekly for the first 5 weeks, and CIS 100 mg/m^2 i.v days 1 and 29) followed by concurrent CTX-RT (CIS 75 mg/m^2 i.v. days 50, 71 and 92) during thoracic RT (63 Gy in 34 fractions during 7 weeks starting day 50)	**Concurrent (HFXRT)** Concurrent CTX and HFXRT starting day 1, total dose 69.6 Gy in 58 fractions during 6 weeks, 1.2 Gy/fraction b.i.d. CTX consisting of CIS 50 mg/m^2 i.v. days 1 and 8 and oral ETOP 50 mg b.i.d. for 10 days only on days of thoracic RT, repeated day 29	
Schild 2002[62]	**Concurrent** Concurrent ETOP (100 mg/m^2) and CIS (30 mg/m^2) days 1–3 and 28–30 during RT. 60 Gy in 30 daily fractions	**Concurrent** Concurrent ETOP (100 mg/m^2) and CIS (30 mg/m^2) days 1–3 and 28–30 during RT. 30 Gy in 20 (1.5-Gy) fractions b.i.d. followed by 14-day break then same again; 6-hour gap between RT doses	
Vokes 2002[47]	**Induction/concurrent** CIS: four cycles 80 mg/m^2 i.v., 30–60 minutes, days 1 and 22 (induction) and days 43 and 64 (concomitant). GEM: during induction CTX (cycles 1 and 2) at 1250 mg/m^2 i.v., 30 minutes, days 1, 8, 22 and 29; during concomitant CTX (cycles 3 and 4) at 600 mg/m^2 i.v., 30 minutes, days 43, 50, 64 and 71. 66 Gy (44 Gy in 22 fractions of 2 Gy/fraction, 22 Gy in 11 fractions of 2 Gy/fraction)	**Induction/concurrent** CIS: same as arm 1. PAX: 225 mg/m^2 i.v. over 3 hours days 1 and 22 during induction (before CIS),135 mg/m^2 i.v. over 3 hours days 43 and 64 (concomitant)	**Induction/concurrent** CIS: same as arm 1. VNB: 25 mg/m^2 i.v. for 12 minutes days 1, 8, 15, 22 and 29 (induction) and 15 mg/m^2 i.v. for 12 minutes days 43, 50, 64 and 71 (concomitant)
Zatloukal 2004[51]	**Concurrent** CIS 80 mg/m^2 day 1, VNB 25 mg/m^2 days 1, 8 and 15 (reduced to 12.5 mg/m^2 during cycles 2 and 3). Cycles repeated every 28 days, maximum four cycles. RT started on day 4 of cycle 2; 60 Gy in 30 fractions, five fractions per week for 6 weeks	**Sequential** CIS 80 mg/m^2 day 1, VNB 25 mg/m^2 days 1, 8 and 15 (reduced to 12.5 mg/m^2 during cycles 2 and 3). Cycles repeated every 28 days, maximum four cycles. RT started within 2 weeks of completion of CTX; 60 Gy in 30 fractions, five fractions per week for 6 weeks	

Study ID	Arm 1	Arm 2	Arm 3
Belani 2005[52]	**Sequential** Two 3-week cycles of PAX 200 mg/m^2 over 3 hours, then CARB AUC 6 mg/ml minute i.v. over 30 minutes. RT day 42,1.8 Gy daily, five times a week (45.0 Gy target dose in 5 weeks to the initial field), followed by a total of 18.0-Gy fractions delivered at 2.0-Gy fractions daily to the initial tumour volume with reduced fields but including enlarged lymph nodes > 2.0 cm (total dose 63.0 Gy in 34 fractions over 7 weeks)	**Induction/concurrent** Induction – same CTX as arm 1, start RT after 2 cycles concurrent with weekly PAX 45 mg/m^2 i.v. over 1 hour followed by CARB AUC 2 mg/ml minute over 30 minutes – RT as for arm 1	**Concurrent/consolidation** RT concurrent with weekly PAX 45 mg/m^2 i.v. over 1 hour followed by CARB AUC 2 mg/ml minute over 30 minutes – RT as for arm 1
Fournel 2005[49]	**Sequential** Induction CTX: CIS 120 mg/m^2 day 1 and VNB 30 mg/m^2 on days 1, 8, 15 and 21, repeated every 4 weeks. RT: for patients with an objective response or no change after CTX, RT began 4 weeks after the third CIS administration. 66 Gy in 33 fractions of 2 Gy each, for 5 days a week over 6.5 weeks	**Concurrent/consolidation** Same RT as arm 1 started day 1 [with 2 concurrent cycles CIS 20 mg/m^2/day and ETOP 50 mg/m^2/day (days 1–5 and days 29–33)]; day 78 consolidation therapy – CIS 80 mg/m^2 on days 78 and 106 and VNB 30 mg/m^2/week from day 78 to day 127	
Reinfuss 2005[46]	**Sequential** Two series of induction CTX (CIS 100 mg/m^2 on day 1; VNB 20 mg/m^2 on days 1 and 8; a 28-day gap between courses). Conformal RT began on day 8 of the second course	**Concurrent** CIS 100 mg/m^2 administered on day 1 and day 36 of irradiation, VNB 20 mg/m^2 on days 1, 8, 36 and 43 of irradiation	
Dasgupta 2006[56]	**Sequential** CIS 80 mg/m^2 day 1 and ETOP 120 mg/m^2 days 1–3 i.v. repeated every 3 weeks for three cycles; 3–4 weeks after the third cycle – RT 6000 cGy/30 fractions and three more cycles of CTX with the same regimen	**Concurrent/consolidation** RT 5000 cGy/25 fractions over 5 weeks with CIS 20 mg/m^2 i.v. days 1–5 and ETOP 50 mg/m^2 i.v. days 1–5. Same schedule repeated after 3 weeks from day 22 to day 26. Day 1 CTX started from first day RT. Then two more cycles of CTX using same drugs and regimen at 3-week intervals	

DOI: 10.3310/hta17060

Study ID	Arm 1	Arm 2	Arm 3
Gouda 2006[59]	**Induction/concurrent** Induction two cycles of PAX 175 mg/m^2 and CARB AUC 6 on days 1 and 28 then concomitant PAX 45 mg/m^2 and CARB AUC 2 weekly with RT (initial large-field target included the primary tumour, the mediastinum at least 5 cm below the carina and ipsilateral supraclavicular region; boost target volume encompassed primary tumour with 2-cm margin; max. dose not to exceed prescribed dose by > 15%)	**Concurrent** Concomitant PAX 45 mg/m^2 and CARB AUC 2 weekly with RT (initial large-field target included the primary tumour, the mediastinum at least 5 cm below the carina and ipsilateral supraclavicular region; boost target volume encompassed primary tumour with 2-cm margin; max. dose not to exceed prescribed dose by > 15%)	
Belderbos 2007[54]	**Sequential** Two courses of GEM 1250 mg/m^2 days 1 and 8 and CIS 75 mg/m^2 day 2 with 3-week interval. Accelerated high-dose conformal RT: 66 Gy in 24 fractions (2.75 Gy/fraction) in 32 days	**Concurrent** Daily low-dose CIS (6 mg/m^2) 1–2 hours before each fraction. RT as for arm 1	
Vokes 2007[48]	**Induction/concurrent** CARB AUC 2 i.v. over 30 minutes and PAX 50 mg/m^2 during 66 Gy of chest RT, started on day 1 at five fractions per week for 7 consecutive weeks at 2 Gy/fraction	**Concurrent** Two cycles of PAX 200 mg/m^2 i.v. over 3 hours and CARB AUC 6 i.v. over 30 minutes every 21 days, concurrent CTX-RT started day 43 (same as arm 1)	
Liu 2008[53]	**Concurrent/consolidation** Low-dose weekly DOC 20 mg/m^2 i.v. for 1 hour and 4 mg DOC i.v. to prevent allergy, concomitant with standard fractionation schedule with 3D conformal RT. Involved-field irradiation; gross tumour and metastatic lymph nodes irradiated to total dose 66–70 Gy. Consolidation CTX with DOC and CIS for no more than four cycles	**Concurrent/consolidation** DOC 60 mg/m^2 day 1 and CIS 30 mg/m^2 days 1–3 every 21 days. DOC 8 mg b.i.d. for successive 3 days as oral medication for allergy, concomitant with standard fractionation schedule with 3D conformal RT. Involved-field irradiation; gross tumour and metastatic lymph nodes irradiated to total dose 66–70 Gy. Consolidation CTX with DOC and CIS for no more than four cycles	

Study ID	Arm 1	Arm 2	Arm 3
Socinski 2008[55]	**Induction/concurrent** Induction CARB i.v. AUC 6 and PAX 225 mg/m^2 i.v. over 3 hours days 1 and 22. Day 43: weekly CARB i.v. AUC 2 and PAX 45 mg/m^2 i.v. for 7 weeks during RT. 74 Gy – 40 Gy to PTV and 34 Gy to boost volume PTV – 2 Gy/day	**Induction/concurrent** Two cycles induction CARB i.v. AUC 5 and GEM 1000 mg/m^2 i.v. over 30 minutes on days 1 and 8 of each cycle. Day 43: twice-weekly GEM 35 mg/m^2 i.v. for 7 weeks during RT (same as arm 1)	
Berghmans 2009[45]	**Induction/concurrent** CIS 60 mg/m^2, GEM 1 g/m^2, days 1 and 8, and VNB 25 mg/m^2, days 1 and 8, with reduced dosage of both during RT (66 Gy). Two cycles of CTX with RT followed by two further cycles of CTX alone	**Concurrent/consolidation** CTX and RT same as arm 1. Two cycles of CTX alone followed by two further cycles of CTX with RT	
Crvenkova 2009[57]	**Sequential** CARB AUC 6 day 1 and ETOP 100 mg/m^2 days 1–3, repeated every 3 weeks. RT began 4 weeks after the fourth cycle of CTX. Conformal RT 60 Gy in 30 fractions of 2 Gy/fraction for 5 days a week for 6 weeks	**Concurrent/consolidation** CIS 30 mg/m^2 and ETOP 100 mg/m^2 days 1–3 for first cycle and second 3-day cycle administered in last 3 days of RT. After 4 weeks of concurrent CTX-RT, two cycles of consolidation CTX began: CARB AUC 6 and ETOP 100 mg/m^2 on days 1–3. Conformal RT same as arm 1	
Nyman 2009[58]	**Induction/concurrent** Induction two cycles of PAX 200 mg/m^2 and CARB AUC 6 then third identical cycle concomitant with start of accelerated RT, 1.7 Gy b.i.d. to 64.6 Gy in 4.5 weeks	**Induction/concurrent** Induction two cycles of PAX 200 mg/m^2 and CARB AUC 6 then daily concomitant PAX 12 mg/m^2 with conventionally fractionated RT, 2 Gy to 60 Gy in 6 weeks	**Induction/concurrent** Induction two cycles of PAX 200 mg/m^2 and CARB AUC 6 then weekly concomitant PAX 60 mg/m^2 and identical RT as arm 2

Study ID	Arm 1	Arm 2	Arm 3
Zhu 2009[60]	**Concurrent** VNB 25 mg/m^2 i.v. days 1 and 8, and CIS 20 mg/m^2 i.v. days 1–5; four cycles, 28 days per cycle. 3D conformal RT Dγ1.8∼2 Gy daily, five times a week. After the total dose reached 50 Gy, reduced fields to the residual tumour and increased dosage of radiation; as far as possible set one fixed field unless the distance of two adjacent lesions was > 2 cm then set as different fields, with total dose Dγ60∼66 Gy	**Sequential** VNB 25 mg/m^2 i.v. days 1 and 8, and CIS 20 mg/m^2 i.v. days 1–5; four cycles, 28 days per cycle. 3D conformal RT same as arm 1	
Movsas 2010[61]	**Concurrent/consolidation** Concurrent CIS 50 mg/m^2 days 1 and 8 plus ETOP 50 mg/m^2 days 1–5 for two 28-day cycles plus RT (62 Gy, 2 Gy daily in 31 fractions over 7 weeks), followed by GEM 1000 mg/m^2 on days 1 and 8 every 21 days for three cycles	**Concurrent/consolidation** Same CTX-RT as arm 1 followed by GEM 1000 mg/m^2 on days 1 and 8 plus DOC 75 mg/m^2 day 1 every 21 days for three cycles	

AUC, area under the curve; b.i.d., twice daily; HFXRT, hyperfractionated RT; i.v., intravenously; PTV, planning target volume; VBL, vinblastine.

Appendix 8 Relative dose intensity

Study ID	Arm 1	Arm 2	Arm 3
Jeremic 2001[63]	NR	NR	
Komaki 2002[50]	58/81 (72%) completed CTX; 49/80 (61%) completed RT per protocol	62/82 (76%) completed CTX; 48/81(59%) completed RT per protocol	
Schild 2002[62]	NR	NR	NR
Vokes 2002[47]	NR	NR	NR
Zatloukal 2004[51]	83% of patients received all four courses of CTX; mean number of CTX courses was 3.65. RT was delivered to 94% of patients; 85% received a dose > 50 Gy (median dose 59.4 Gy)	58% of patients received all four courses of CTX; mean number of CTX courses was 3.14. RT was delivered to 64% of patients; 60% received a dose > 50 Gy (median dose 60 Gy). A significantly higher proportion of patients ($p = 0.0002$) received RT in the concurrent schedule (arm 1). The number of patients who completed four cycles of CTX was also significantly higher in arm 1 ($p = 0.007$). The number of CTX courses administered was not significantly different between arms	
Belani 2005[52]	95% of patients received planned two cycles of induction CTX; 76% received scheduled RT dose	93% of patients received planned two cycles of induction CTX; during concurrent CTX-RT 46% received seven weekly cycles of CTX; 65% completed at least six cycles; 70% received scheduled RT dose	During concurrent CTX-RT 70% of patients received seven weekly cycles of CTX; 85% completed at least six cycles; 81% received scheduled RT dose; 67% received planned two cycles of consolidation CTX
Fournel 2005[49]	59.4% of patients received at least 60 Gy RT; 23% received less than three cycles	88% of patients received at least 60 Gy RT ($p < 0.001$); 54% received two planned cycles of consolidation CTX, 7% received only one course, 39% received no consolidation CTX	

Study ID	Arm 1	Arm 2	Arm 3
Reinfuss 2005[46]	Complete combined modality treatment had been administered to 86/89 patients (96.6%). This difference achieves extreme statistical significance (log-rank test $p < 0.01$). Because of toxicity treatment was not completed in 2.2% of patients	Complete combined modality treatment had been administered to 63/84 patients (75%). This difference achieves extreme statistical significance (log-rank test $p < 0.01$). There was statistically significantly higher toxicity of concurrent treatment than sequential treatment. Because of this toxicity the treatment was not completed in 21.4% of patients	
Dasgupta 2006[56]	RT interrupted in four patients (11%); CTX not altered, modified or delayed for any patient	RT interrupted in six patients (17%); CTX not altered, modified or delayed for any patient	
Gouda 2006[59]	NR	NR	
Belderbos 2007[54]	97.4% started protocol treatment. Full-dose CTX 84%; full-dose RT 97%. Overall treatment time RT 32 (12–42) days	82.5% started protocol treatment. Full-dose CTX 82%; full-dose RT 97%. Overall treatment time RT 32 (22–38) days	
Vokes 2007[48]	NR by arm	NR by arm	NR by arm
Liu 2008[53]	Both groups completed concurrent CTX-RT. At the following consolidation CTX three cases were withdrawn (one progressed, two decided to quit). Four, seven and eight patients received two, three and four cycles respectively; therefore, 19 cases completed follow-up and survival analysis	Both groups completed concurrent CTX-RT. At the following consolidation CTX one patient dropped out because of disease progression. Five patients received three cycles of treatment and 16 patients received four cycles of treatment; therefore, 21 cases completed follow-up and survival analysis	

Study ID	Arm 1	Arm 2	Arm 3
Socinski 2008[55]	During induction CTX 95% of patients completed both cycles. Initiation of concurrent CTX beginning on day 43 was accomplished in 92.8% of patients. During concurrent CTX-RT 76% of patients completed all seven weekly treatments of CARB and PAX. A total of 92.8% received combined CTX-RT. Median volume of lung receiving 20 Gy (V20) was 32% (range 18–52%). Median dose of TRT delivered was 74 Gy with an average dose delivered of 72.7 Gy (range 34.0–77.9 Gy); 87.2% completed therapy to at least 74 Gy	During induction CTX 92% of patients completed both cycles. Initiation of concurrent CTX beginning on day 43 was accomplished in 88.4% of patients. During concurrent CTX-RT 69% of patients completed all 7 weeks of twice-weekly GEM. A total of 88.4% received combined CTX-RT. Median volume of lung receiving 20 Gy (V20) was 32% (range 20–50%). Median dose of TRT delivered was 74 Gy with an average dose delivered of 70.6 Gy (range 22.0–77.7 Gy); 78.3% completed therapy to at least 74 Gy	
Berghmans 2009[45]	62% of patients completed protocol treatment; median duration of whole treatment 100 days; RDI for CIS 65%, GEM 61% and VNB 61%. One patient did not start RT; total RT dose 60–66 Gy; median duration of RT 46 days (27–53 days)	86% of patients completed protocol treatment; median duration of whole treatment 95 days; RDI for CIS 82% ($p = 0.02$), GEM 80% ($p < 0.001$) and VNB 79% ($p < 0.001$). Three patients did not start RT; total RT dose 60–66 Gy; median duration of RT 46 days (43–67 days)	
Crvenkova 2009[57]	NR	NR	
Nyman 2009[58]	NR	NR	
Zhu 2009[60]	The required time for completing treatments was statistically significantly different between the two groups; on average the concurrent group took 31 days less than the sequential group ($p < 0.05$)	The required time for completing treatments was statistically significantly different between the two groups; on average, the concurrent group took 31 days less than the sequential group ($p < 0.05$)	
Movsas 2010[61]	78.0% of patients proceeded to consolidation therapy with 32 patients receiving GEM; 90.6% received all three planned cycles of GEM	78.0% of patients proceeded to consolidation therapy with 32 patients receiving GEM + DOC; 68.8% received all three planned cycles of GEM + DOC	

NR, not reported; TRT, thoracic radiation therapy.

Appendix 9 Patient characteristics

Study ID	Intervention	No. randomised	Median age (years)	Male (%)	Disease stage		Histology		PS (%)	
					IIIA (%)	IIIB (%)	Squamous cell carcinoma (%)	Adenocarcinoma (%)		
Jeremic 2001[63]	CTX + RT days 1–5	99	59	64	52	48	NR	NR	KPS	50 = 8, 60 = 9, 70 = 11, 80 = 24, 90 = 30, 100 = 17
	CTX + RT days 1–7	99	59	67	54	46	NR	NR	KPS	50 = 8, 60 = 9, 70 = 9, 80 = 23, 90 = 29, 100 = 21
Komaki 2002[50]	CTX → CTX + RT	NR	NR	72	35	64	43	30	KPS	70–80 = 27, 90–100 = 73
	CTX + (HFX)RT	NR	NR	59	33	66	40	35	KPS	70–80 = 23, 90–100 = 77
Schild 2002[62]	CTX + RT (2×daily)	121	64	62	51	49	35	NR	ECOG	0 = 49, 1 = 51
	CTX + RT (4×daily)	125	64	62	54	46	38	NR	ECOG	0 = 50, 1 = 50
Vokes 2002[47]	CTX → CTX + RT	NR	62	66	63	37	29	34	CALGB	0 = 53, 1 = 47
	CTX → CTX + RT	NR	64	66	52	48	29	45	CALGB	0 = 53, 1 = 47
	CTX → CTX + RT	NR	58	76	40	60	42	33	CALGB	0 = 51, 1 = 49
Zatloukal 2004[51]	CTX + RT	52	62	63	15	85	46	23	WHO	0 = 29, 1 = 63, 2 = 8
	CTX → RT	50	61	72	14	86	44	30	WHO	0 = 32, 1 = 64, 2 = 4
Belani 2005[52]	CTX → RT	97	NR	67	35	62	42	35	KPS	70 = 8, 80–100 = 92
	CTX → CTX + RT	80	NR	73	36	64	32	34	KPS	70 = 7, 80–100 = 93
	CTX + RT → CTX	99	NR	67	38	62	40	35	KPS	70 = 2, 80–100 = 98

Study ID	Intervention	No. randomised	Median age (years)	Male (%)	Disease stage		Histology		PS (%)	
					IIIA (%)	IIIB (%)	Squamous cell carcinoma (%)	Adenocarcinoma (%)		
Fournel 2005[49]	CTX → RT	106	56	90	18	80	55	30	ECOG	0 = 56, 1 = 45
	CTX + RT → CTX	106	57	85	88	67	60	23	ECOG	0 = 51, 1 = 49
Reinfuss 2005[46]	CTX → RT	89	NR	72	33	67	69	31	KPS	70–80 = 84, 90 = 16
	CTX + RT	84	NR	71	33	67	67	32	KPS	70–80 = 85, 90 = 15
Dasgupta 2006[56]	CTX → RT	35	58	NR	69	31	63	31	KPS	60 = 3, 70 = 31, 80 = 51, 90 = 14
	CTX + RT	36	57	NR	67	33	50	33	KPS	60 = 6, 70 = 22, 80 = 56, 90 = 17
Gouda 2006[59]	CTX → CTX + RT	20	61	90	30	70	55	35	ECOG	0 = 15, 1 = 85
	CTX + RT	20	62	75	15	85	70	25	ECOG	0 = 5, 1 = 95
Belderbos 2007[54]	CTX → RT	78	64	100	45	47	40	32	WHO	0 = 42, 1 = 58
	CTX + RT	80	62	93	30	64	40	24	WHO	0 = 44, 1 = 56
Vokes 2007[48]	CTX + RT	182	63	69	48	46	NR	NR	CALGB	0 = 45, 1 = 52
	CTX → CTX + RT	184	64	63	49	48	NR	NR	CALGB	0 = 44, 1 = 56
Liu 2008[53]	Low-dose weekly CTX (DOC) + RT (3D conformal) → CTX (DOC + CIS)	22	53	73	45	55	36	50	ECOG	0 = 36, 1 = 64
	Systemic CTX + RT (3D conformal) → CTX (DOC + CIS)	22	60	82	36	64	55	36	ECOG	0 = 23, 1 = 77
Socinski 2008[55]	CTX → RT + CTX	43	62	74	38	38	36	40	ECOG	0 = 48, 1 = 52
	CTX → RT + CTX	26	58	77	38	62	35	27	ECOG	0 = 38, 1 = 62

Study ID	Intervention	No. randomised	Median age (years)	Male (%)	Disease stage		Histology		PS (%)	
					IIIA (%)	IIIB (%)	Squamous cell carcinoma (%)	Adenocarcinoma (%)		
Berghmans 2009[45]	CTX + RT → CTX	26	55	86	19	76	33	43	KPS	60–70 = 14, 80–100 = 86
	CTX → CTX + RT	29	61	89	32	68	29	43	KPS	60–70 = 7, 80–100 = 93
Crvenkova 2009[57]	CTX → RT	NR	45	89	NR	NR	76	13	NS	0 = 62, 1 = 38
	CTX + RT → CTX	NR	40	88	NR	NR	55	25	NS	0 = 68, 1 = 32
Nyman 2009[58]	CTX → CTX + accelerated RT	NR	63 (mean)	51	35	65	27	51	WHO	0 = 26, 1 = 22
	CTX → CTX daily + conventional RT	NR	63 (mean)	44	32	68	32	46	WHO	0 = 27, 1 = 22
	CTX → CTX weekly + conventional RT	NR	61 (mean)	60	35	65	35	44	WHO	0 = 27, 1 = 24
Zhu 2009[60]	CTX + RT (3D conformal)	NR	60	75	NR	NR	43	52	NR	NR
	CTX → RT (3D conformal)	NR	59	76	NR	NR	40	52	NR	NR
Movsas 2010[61]	CTX + RT → CTX	32	59.5	53	16	81	50	38	ECOG	0 = 34, 1 = 66
	CTX + RT → CTX	32	59.5	81	34	59	53	30	ECOG	0 = 41, 1 = 59

HFX, hyperfractionated; NR, not reported.

Appendix 10 Inclusion/exclusion criteria of included studies

Study ID	Inclusion criteria	Exclusion criteria
Jeremic 2001[63]	Age ≥ 18 years, histologically or cytologically confirmed advanced NSCLC classified as stage IIIA or IIIB by the UICC, a KPS score of at least 50% and no previous therapy	Postoperative thoracic recurrence or a history of any previous or concurrent cancer (except that of the skin) unless the patient had shown no evidence of disease for > 5 years. Patients with malignant pleural effusion were also excluded
Komaki 2002[50]	At least 18 years old and histologically or cytologically confirmed diagnosis of NSCLC, classified as medically inoperable stage II tumours or locally unresectable stage IIIA or IIIB disease according to the American Joint Committee on Cancer. The primary tumour and/or regional lymph node metastases had to be measurable or at least able to be evaluated by imaging studies. The KPS was required to be ≥ 70 and weight loss was limited to ≤ 5% in the 3 months before the diagnosis	Patients with pleural effusion or distant metastases were not eligible. Patients were excluded if they had had previous invasive malignant tumours other than squamous or basal cell carcinoma of the skin within 5 years of randomisation or previous RT or CTX
Schild 2002[62]	Patients must have been diagnosed with unresectable stage III NSCLC that had not spread beyond the site of origin or ipsilateral hilum, mediastinum or ipsilateral supraclavicular nodes. If bilateral mediastinal adenopathy was present the disease had to be encompassable within reasonable off-cord oblique boost fields. All patients had a pretreatment absolute neutrophil count > 1500/μl, a platelet count > 100,000/μl, serum creatinine level < 1.5 times the upper limit of normal, FEV_1 > 1 l or > 40% of the predicted value, and an ECOG PS of 0 or 1	Myocardial infarction within the past 3 months, uncontrolled congestive heart failure, uncontrolled arrhythmia, more than a minimal pleural effusion, previous CTX or RT for this malignancy, weight loss > 5% within the past 3 months, pregnant or lactating women
Vokes 2002[47]	Had histological or cytological documentation of NSCLC, including squamous cell carcinoma, adenocarcinoma (including bronchoalveolar cell carcinoma) and large cell and anaplastic carcinoma (including giant- and clear-cell carcinomas). Patients included those who had unresectable or inoperable stage III disease, including N2–N3 disease and any T stage, or those with T4 disease and any nodal stage. Patients with N3 disease were eligible if all gross disease could be encompassed in the radiation boost field. All patients had measurable or assessable disease as measured by chest radiography, CT or MRI performed within 28 days of registration. Assessable lesions included ill-defined masses associated with postobstructive changes or mediastinal or hilar lymphadenopathy measurable only in one dimension. All patients were seen by a radiation oncologist before registration onto the study. Additional eligibility criteria included a CALGB PS of 0–1, weight loss of < 5% in the 3 months before diagnosis, a life expectancy > 2 months, age ≥ 18 years. Required initial laboratory tests included an absolute granulocyte count of 1800/μl, haemoglobin level 10 g/dl, platelet count of 100,000/μl, serum creatinine 1.5 times the upper limit of normal or a 24-hour creatinine clearance of at least 60 ml/minute. In addition, liver function tests had to be 1.5 times the upper limit of normal and the FEV_1 had to be > 800 ml	Patients with stage T3N0 or N1 were not eligible. Patients with scalene, supraclavicular or contralateral hilar lymph node involvement or direct invasion of the vertebral body or with a pleural effusion that was exudative, bloody or cytologically proven to contain malignant cells were ineligible. Patients with completely resected tumours, who were pregnant or who had previously received CTX or RT were also excluded
Zatloukal 2004[51]	Histologically or cytologically confirmed diagnosis of inoperable IIIA or IIIB NSCLC suitable for radical RT, WHO/ECOG PS 0–2, a measurable or evaluable neoplastic lesion according to WHO criteria, adequate bone marrow	Previous CTX or RT, history of other malignancy (except for in situ cervical carcinoma or non-melanoma skin carcinoma), pregnancy

Study ID	Inclusion criteria	Exclusion criteria
Belani 2005[52]	Histological or cytological determination of stage IIIA or IIIB NSCLC (including squamous cell carcinoma, adenocarcinoma, large cell anaplastic carcinoma and poorly differentiated NSCLC) was required. Patients with T1–T3 with N2 disease if medically inoperable, T4 with any node size and extent, and N3 disease with any tumour involvement were eligible. Patients were required to have measurable disease, be aged > 18 years and to have a KPS > 70%, weight loss < 10% in the 3 months before diagnosis, granulocyte count 2000/ml, platelet count 100,000/ml, haemoglobin level > 8 mg/dl, bilirubin level < 1.5 times the upper limit of normal, creatinine clearance > 50 ml/minute and FEV_1 > 800 ml	Significant pleural effusions, previous systemic CTX, previous RT to the thorax or total surgical resection, brain metastases, active concurrent malignancy, serious medical or psychiatric illness, history of serious cardiac disease
Fournel 2005[49]	Age 18–70 years, ECOG PS ≤ 1, ≤ 10% weight loss in the 3 months before inclusion, previously untreated histologically or cytologically proven NSCLC, unresectable stage IIIA–N2 disease or stage IIIB disease without pleural involvement, neutrophils 1500/μl, platelets 100,000/μl, AST and ALT 2 times the upper limit of the institutional normal range, total bilirubin 1.25 times the upper limit of the institutional normal range and creatinine concentration 120 mol/l. One unidimensionally measurable target lesion 2 cm by CT scan. Adequate pulmonary function was required, with FEV_1 40% of normal and partial arterial oxygen pressure 60 mmHg	Active uncontrolled infection or a fever > 38.3°C, unstable cardiovascular disease, previous malignancy (except for in situ carcinoma of the cervix or adequately treated cutaneous basal or squamous cell carcinoma)
Reinfuss 2005[46]	Microscopically confirmed NSCLC not qualifying for surgical treatment, age < 70 years, grade of malignancy III°A (N2 feature) and III°B acc. To TNM without pleural effusion, KPS ≥ 70, decrease in body weight not exceeding 5% of calculated body mass, haemoglobin level > 11 g/dl, white blood cell count > 4000/μl, platelet count > 150,000/μl, no respiratory insufficiency: spirometry and blood gas analysis values as for radical RT, adequate hepatic and renal function (in biochemical analysis), no circulatory insufficiency (on clinical examination and ECG), no previous history of malignancy, no previous causative treatment	
Dasgupta 2006[56]	Patients up to 75 years at diagnosis, KPS ≥ 60, absence of distant metastasis, no previous therapy for cancer and no haematological, cardiac, renal or liver function abnormalities contraindicating combined modality therapy	
Gouda 2006[59]	Histologically documented stage IIIA or IIIB disease, measurable or assessable disease, age > 18 years, ECOG PS ≤ 1, weight loss < 10% during the 6 months preceding diagnosis, no previous CTX or lung RT, platelet count > 100,000/μl, absolute neutrophil count > 1800/μl, haemoglobin level > 10 g/dl, blood urea nitrogen < 1.5 times the upper limit of normal, creatinine level < 1.5 mg/dl, bilirubin < 1.5 times the upper limit of normal, AST < 2 times the upper limit of normal, no other serious medical or psychiatric illness	Patients with malignant pleural effusions were not eligible
Belderbos 2007[54]	Patients with inoperable NSCLC stage T1–4N0–3 disease (excluding N3 disease based on supraclavicular nodes). All patients had good prognostic features (weight loss < 10% in the preceding 3 months and WHO PS 0 or 1). All patients had a FEV_1 ≥ 1 l and a diffusion capacity of at least 60%	
Vokes 2007[48]	Histological or cytological documentation of NSCLC. Patients had previously untreated, unresectable or inoperable stage III disease. Patients with N3 disease were eligible if all gross disease could be encompassed in the radiation boost field. All patients had measurable or assessable disease, CALGB PS of 0–1, life expectancy > 2 months, age ≥ 18 years, forced expiratory volume in 1 second > 800 ml	Patients with scalene, supraclavicular or contralateral hilar lymph node involvement, with direct invasion of the vertebral body or with a pleural effusion. Also, pregnancy or previous surgery

Study ID	Inclusion criteria	Exclusion criteria
Liu 2008[53]	NR	NR
Socinski 2008[55]	Histological or cytological diagnosis of stage IIIA or IIIB NSCLC, ECOG PS of 0–1, absolute neutrophil count 1500/μl, platelet count 100,000/μl, haemoglobin level 10 g/dl, calculated creatinine clearance (estimated by the Cockcroft–Gault formula) 20 ml/minute, AST < 2 times the upper limit of institutional normal, bilirubin < 1.5 mg/dl, FEV_1 had to be > 1.2 l	Palpable supraclavicular adenopathy, malignant pleural effusions or direct invasion of vertebral bodies. Also, previous CXT for lung cancer or RT to the chest
Berghmans 2009[45]	Previously untreated initially unresectable (or inoperable for medical reasons) non-metastatic NSCLC (histologically or cytologically confirmed) without homolateral malignant pleural effusion and homolateral (except for upper lobe lesion) or heterolateral supraclavicular lymph node involvement; no functional or anatomical contraindication to chest irradiation; an assessable or measurable lesion had to be present. Patients should not have a previous history of malignancy except non-melanoma skin cancer or in situ carcinoma of the cervix and 'cured' malignant tumour (> 5-year disease-free interval). Other eligibility criteria included KPS ≥ 60 and good renal (serum creatinine level ≤ 1.5 mg/dl and/or creatinine clearance > 60 ml/minute), hepatic (serum bilirubin level ≤ 1.5 mg/dl) and haematological (neutrophil count ≥ 2000/μl and platelet count ≥ 100,000/μl) functions	Patients presenting with recent (< 3 months before the date of treatment) myocardial infarction, active congestive heart failure or cardiac arrhythmia requiring medical treatment, uncontrolled infectious disease, symptomatic polyneuropathy or other serious medical or psychiatric illness precluding adherence to the study
Crvenkova 2009[57]	Aged between 18 and 70 years, ECOG PS ≤ 1 and ≤ 10% weight loss in the 3 months before inclusion. Patients had to have previously untreated histologically or cytologically proven NSCLC with unresectable stage IIIA–N2 disease or stage IIIB disease without pleural effusion. Stage IIIB disease was assigned either by N3 (contralateral mediastinal or supraclavicular nodes) or by T4 from invasion of mediastinal structures. The following laboratory values were required: leucocytes ≥ 1.5×10^3/l, platelets ≥ 100 × 10/l, AST and ALT ≤ 2 times the upper limit of the referent range (data reproduced exactly as given in publication)	Uncontrolled infection or a fever > 38°C, unstable cardiovascular disease and previous malignancy
Nyman 2009[58]	Non-resectable or medically inoperable patients with histologically or cytologically confirmed NSCLC stage IIIA or IIIB disease according to the TNM classification. There must be at least one bidimensional measurable lesion on CT scan. Patients must be > 18 years and have a PS of 0–1 according to the WHO scale and a lung function with FEV_1 ≥ 1 l or ≥ 40% of the expected volume. White blood cell count should exceed 3000/μl, granulocyte count 1500μl and platelet count 100,000/μl. Creatinine clearance measured by chromium-ethylenediaminetetraacetic acid (Cr-EDTA) or iohexol should exceed 40 ml/minute and bilirubin should be ≤ 1.5 times the upper normal limit	Stage IIIB with malignant pleural effusion, any history of breast cancer and malignant melanoma or history of other malignancy treated within the last 5 years, significant history of cardiac disease, serious active infection and previous treatment with CTX or RT for the present disease
Zhu 2009[60]	Diagnosed as stage IIIA/IIIB (UICC 2002) on pathology and cytology, and also by chest CT, brain CT, ECT (electrochemical tumour therapy?) and abdominal ultrasound before receiving treatments. In all selected patients white blood cells count ≥ 4000/μl, platelet count ≥ 80,000/μl, no significant hepatic or renal dysfunction, electrocardiogram normal and KPS ≥ 80. Patients with no previous cancer history or no serious medical disease that may affect the completion of the scheduled treatment plan were included	

Study ID	Inclusion criteria	Exclusion criteria
Movsas 2010[61]	Patients had histological or cytological proof of a single, primary bronchogenic NSCLC. Pathological diagnosis from involved mediastinal or supraclavicular lymph nodes alone was accepted if a distinct primary lesion was evident on radiographs. Patients with two distinct parenchymal primary lesions were ineligible. Inoperable stage IIIA disease was determined by the presence of multiple or bulky N2 mediastinal lymph nodes. Stage IIIB disease was determined either by N3 involvement from pathologically documented contralateral mediastinal or by supraclavicular nodes not extending into the cervical region or by T4 invasion of mediastinal structures, including the heart, great vessels, trachea, carina, oesophagus or vertebral body. Patients who had a separate satellite nodule in the same lobe as the primary lesion (T4/stage IIIB disease) were eligible if the nodule could be encapsulated within a tolerable radiation portal. Initial staging included brain imaging (either CT or MRI) and a bone scan. Patients with pleural effusions were eligible only if there was negative cytology or the effusion was inaccessible to thoracentesis. Patients with pericardial effusions or weight loss of 10% within the previous 6 months were ineligible. Patients were required to have measurable disease by chest radiography or CT scan. Previous CTX or RT for lung cancer was not permitted. Previous exploratory diagnostic surgery was permitted. Pulmonary function requirements included a FEV_1 of 1 l by spirometry. Organ function requirements included an absolute neutrophil count of 1500/μl, platelet count of 100,000/μl, serum bilirubin 1.5 mg/dl and serum glutamic oxaloacetic transaminase 1.5 times the institutional upper limits of normal (IULN), unless the abnormality was caused by documented benign disease. Patients with benign disease required a serum glutamic oxaloacetic transaminase $<$ 2.5 times the IULN and alkaline phosphatase 2.5 times the IULN. Patients were also required to have adequate organ and bone marrow function including an estimated creatinine clearance of 50 ml/minute (using the modified Cockcroft–Gault formula). Patients were required to be 18 years of age	Patients who were breastfeeding or pregnant or who had serious concomitant disorders were ineligible

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FEV_1, forced expiratory volume in 1 second; MRI, magnetic resonance imaging.

Appendix 11 Adverse events

Study ID	Adverse event	Arm 1 (%)	Arm 2 (%)	Arm 3 (%)
Jeremic 2001[63]	*Haematological toxicity*			
	Leucopenia	G3–4 = 7	G3–4 = 13	
	Thrombocytopenia	G3–4 = 5	G3–4 = 14	
	Anaemia	NR	G3 = 1	
	Non-haematological toxicity			
	Acute			
	Bronchopulmonary	G3–4 = 12	G3–4 = 13	
	Oesophageal	G3–4 = 15	G3–4 = 17	
	Haematological	G3–4 = 12	G3–4 = 0	
	Osseous	G3–4 = 0	G3–4 = 0	
	Gastric	G3–4 = 2	G3–4 = 3	
	Late			
	Bronchopulmonary	G3–4 = 9	G3–4 = 8	
	Oesophageal	G3–4 = 9	G3–4 = 8	
	Haematological	G3–4 = 0	G3–4 = 0	
	Osseous	G3–4 = 0	G3–4 = 0	
	Gastric	G3–4 = 3	G3–4 = 3	
	Toxic deaths (*n*)	NR	NR	
Komaki 2002[50]	*Haematological toxicity*			
	Anaemia	G3–4 = 10	G3–4 = 11	
	Other haematological	G3–4 = 78	G3–4 = 66	
	Non-haematological toxicity			
	Lung	G3–4 = 4	G3–4 = 9	
	Nausea/vomiting	G3–4 = 14	G3–4 = 24	
	Oesophagitis	G3–4 = 6	G3–4 = 37	
	Toxic deaths (*n*)	Unclear	Unclear	

Study ID	Adverse event	Arm 1 (%)	Arm 2 (%)	Arm 3 (%)
Schild 2002[62]	*Haematological toxicity*			
	Leucopenia	G3–4 = 78	G3–4=79	
	Thrombocytopenia	G3–4 = 29	G3–4=19	
	Non-haematological toxicity			
	Nausea	G3–4 = 23	G3–4 = 24	
	Vomiting	G3–4 = 19	G3–4 = 17	
	Oesophagitis	G3–4 = 20	G3–4 = 18	
	Pneumonitis	G3–4 = 11	G3–4 = 15	
	Dyspnoea	G3–4 = 7	G3–4 = 12	
	Toxic deaths (*n*)	3	2	
Vokes 2002[47]	*Haematological toxicity*			
	Platelets	G3 = 33, G4 = 23	G3 = 2, G4 = 4	G3 = 0, G4 = 2
	Haemoglobin	G3 = 30, G4 = 2	G3 = 4, G4 = 0	G3 = 19, G4 = 0
	Granulocytes	G3 = 33, G4 = 18	G3 = 29, G4 = 24	G3 = 19, G4 = 8
	Lymphocytes	G3 = 17, G4 = 62	G3 = 12, G4 = 67	G3 = 21, G4 = 44
	Non-haematological toxicity			
	Oesophagitis	G3 = 35, G4 = 17	G3 = 35, G4 = 4	G3 = 13, G4 = 12
	Dyspnoea	G3 = 12, G4 = 2	G3 = 12, G4 = 8	G3 = 10, G4 = 10
	Acute respiratory distress syndrome	G3–4 = 0	G3 = 4, G4 = 0	G3 = 0, G4 = 2
	Nausea	G3 = 23, G4 = 3	G3 = 14, G4 = 0	G3 = 17, G4 = 2
	Vomiting	G3 = 8, G4 = 7	G3 = 8, G4 = 8	G3 = 2, G4 = 6
	Anorexia	G3 = 22, G4 = 5	G3 = 22, G4 = 0	G3 = 10, G4 = 2
	Toxic deaths (*n*)	0	2	1

Study ID	Adverse event	Arm 1 (%)	Arm 2 (%)	Arm 3 (%)
Zatloukal 2004[51]	*Haematological toxicity*			
	Anaemia	G3–4 = 12	G3–4 = 6	
	Leucopenia	G3–4 = 53	G3–4 = 19	
	Neutropenia	G3–4 = 65	G3–4 = 40	
	Thrombocytopenia	G3–4 = 6	G3–4 = 4	
	Febrile neutropenia	G3–4 = 8	G3–4 = 2	
	Non-haematological toxicity			
	Oesophagitis	G3–4 = 18	G3–4 = 4	
	Hepatotoxicity	G3–4 = 2	G3–4 = 2	
	Renal toxicity	G3–4 = 2	G3–4 = 2	
	Nausea/vomiting	G3–4 = 39	G3–4 = 15	
	Neurotoxicity	G3–4 = 4	G3–4 = 2	
	Cardiotoxicity	G3–4 = 2	G3–4 = 0	
	Pulmonary toxicity	G3–4 = 4	G3–4 = 2	
	Toxic deaths (*n*)	0	0	
Belani 2005[52]	*Haematological toxicity*			
	Anaemia	G3–4 = 3	G3–4 = 75	G3–4 = 10
	Leucopenia	G3–4 = 2	G3–4 = 31	G3–4 = 51
	Granulocytopenia	G3–4 = 0	G3–4 = 16	G3–4 = 26
	Thrombocytopenia	G3–4 = 0	G3–4 = 9	G3–4 = 12
	Non-haematological toxicity			
	Cardiac	G3–4 = 3	G3–4 = 3	G3–4 = 8
	Oesophagitis	G3–4 = 3	G3–4 = 19	G3–4 = 28
	Lung	G3–4 = 6	G3–4 = 4	G3–4 = 16
	Neurological	G3–4 = 4	G3–4 = 7	G3–4 = 11
	Hyperglycaemia	G3–4 = 1	G3–4 = 4	G3–4 = 9
	Nausea/vomiting	G3–4 = 0	G3–4 = 8	G3–4 = 7
	Toxic deaths (*n*)	0	1	2

Study ID	Adverse event	Arm 1 (%)	Arm 2 (%)	Arm 3 (%)
Fournel 2005[49]	*Haematological toxicity*			
	Neutropenia	G3–4 = 88	G3–4 = 77	
	Anaemia	G3–4 = 28	G3–4 = 20	
	Thrombocytopenia	G3–4 = 15	G3–4 = 16	
	Infection	G3–4 = 12	G3–4 = 14	
	Non-haematological toxicity			
	Infection	G3–4 = 12	G3–4 = 14	
	Peripheral neuropathy	G3 = 4	G3–4 = 0	
	Oesophagitis	G3–4 = 3	G3 = 32	
	Nausea/vomiting	G3–4 = 18	G3–4 = 24	
	Pneumonitis	G3–4 = 11	G3–4 = 5	
	Toxic deaths [*n* (%)]	6 (5.6)	10 (9.5)	
Reinfuss 2005[46]	Haematological toxicity	NR	NR	
	Non-haematological toxicity	NR	NR	
	Toxic deaths (*n*)	2	2	
Dasgupta 2006[56]	Haematological toxicity	NR	NR	
	Non-haematological toxicity			
	Cutaneous	G3 = 17	G3 = 19	
	Mucous membrane	G3 = 0	G3 = 11	
	Upper gastrointestinal	G3 = 6	G3 = 17	
	Toxic deaths (*n*)	NR	NR	
Gouda 2006[59]	Haematological toxicity			
	Neutropenia	G3–4 = 30	G3–4 = 25	
	Thrombocytopenia	G3–4 = 25	G3–4 = 10	
	Anaemia	G3–4 = 5	G3–4 = 45	
	Non-haematological toxicity			
	Oesophagitis	G3–4 = 30	G3–4 = 25	
	Fatigue	G3–4 = 5	G3–4 = 0	
	Nausea/vomiting	G3–4 = 10	G3–4 = 5	
	Myalgia	G3–4 = 15	G3–4 = 5	
	Neuropathy	G3–4 = 10	G3–4 = 5	
	Diarrhoea	G3–4 = 5	G3–4 = 0	
	Alopecia	G3–4 = 5	G3–4 = 0	
	Toxic deaths (*n*)	NR	NR	

Study ID	Adverse event	Arm 1 (%)	Arm 2 (%)	Arm 3 (%)
Belderbos 2007[54]	*Haematological toxicity*			
	Thrombocytopenia	G3–4 = 6	G3–4 = 0	
	Leucopenia	G3–4 = 6	G3–4 = 3	
	Granulocytopenia	G3–4 = 21	G3–4 = 2	
	Acute haematological toxicity	G3–4 = 30	G3–4 = 6	
	Non-haematological toxicity			
	Nausea	G3 = 7	G3 = 6	
	Oesophagitis	G3–4 = 5	G3–4 = 14	
	Shortness of breath	G3–4 = 8	G3–4 = 9	
	Lethargy	G3 = 5	G3 = 6	
	Infection	G3–4 = 5	G3–4 = 5	
	Vomiting	G3–4 = 4	G3–4 = 6	
	Late toxicity, lung	G3–4 = 14	G3–4 = 18	
	Oesophagitis	G3–4 = 4	G3–4 = 5	
	Toxic deaths (*n*)	NR	NR	
Vokes 2007[48]	*Haematological toxicity*			
	Absolute neutrophil count	G3 = 11, G4 = 4	G3 = 24, G4 = 7	
	White blood cell	G3 = 32, G4 = 4	G3 = 38, G4 = 6	
	Haemoglobin	G3 = 5, G4 = 0	G3 = 12, G4 = 0	
	Lymphopenia	G3 = 55, G4 = 8	G3 = 47, G4 = 9	
	Febrile neutropenia	G3 = 2, G4 = 0	G3 = 4, G4 = 0	
	Non-haematological toxicity			
	Fatigue	G3 = 19, G4 = 1	G3 = 17, G4 = 4	
	Anorexia	G3 = 15, G4 = 5	G3 = 11, G4 = 8	
	Dysphagia–oesophageal	G3 = 30, G4 = 2	G3 = 28, G4 = 8	
	Dyspnoea	G3 = 11, G4 = 3	G3 = 15, G4 = 4	
	Pneumonitis	G3 = 3, G4 = 1	G3 = 8, G4 = 2	
	Maximum toxicity	G3 = 58, G4 = 26	G3 = 55, G4 = 30	
	Toxic deaths (*n*)	0	1	

Study ID	Adverse event	Arm 1 (%)	Arm 2 (%)	Arm 3 (%)
Liu 2008[53]	*Haematological toxicity*			
	Neutropenia	G3–4 = 26	G3–4 = 14	
	Anaemia	G3–4 = 0	G3–4 = 0	
	Thrombocytopenia	G3–4 = 10	G3–4 = 0	
	Non-haematological toxicity			
	Oesophagitis	G3–4 = 16	G3–4 = 29	
	Pneumonitis	G3–4 = 5	G3–4 = 10	
	Nausea/vomiting	G3–4 = 16	G3–4 = 43	
	Allergy	G3–4 = 0	G3–4 = 0	
	Asthenia	G3–4 = 0	G3–4 = 0	
	Toxic deaths (*n*)	NR	NR	
Socinski 2008[55]	*Haematological toxicity*			
	Neutropenia	G3 = 30	G3 = 0	
	Thrombocytopenia	G3 = 30	G3 = 0	
	Anaemia	G3 = 14	G3 = 13	
	Non-haematological toxicity			
	Oesophagitis	G3 = 16	G3 = 39	
	Nausea	G3 = 8	G3 = 4	
	Vomiting	G3 = 5	G3 = 0	
	Dehydration	G3 = 5	G3 = 13	
	Weight loss	G3 = 11	G3 = 9	
	Fatigue	G3 = 8	G3 = 35	
	Infection without neutropenia	G3 = 16	G3 = 13	
	Pulmonary	G3 = 0	G3 = 30	
	Cardiac	G3 = 0	G3 = 4	
	Oedema	G3 = 0	G3 = 9	
	Toxic deaths (*n*)	NR	NR	
Berghmans 2009[45]	*Haematological toxicity*			
	Leucopenia	G3–4 = 55	G3–4 = 21	
	Thrombocytopenia	G3–4 = 20	G3–4 = 11	
	Non-haematological toxicity			
	Stomatitis	G3–4 = 5	G3–4 = 4	
	Infection	G3–4 = 20	G3–4 = 4	
	Oesophagitis	G3–4 = 15	G3–4 = 7	
	Alopecia	G3–4 = 0	G3–4 = 4	
	Toxic deaths (*n*)	1	2	

Study ID	Adverse event	Arm 1 (%)	Arm 2 (%)	Arm 3 (%)
Crvenkova 2009[57]	*Haematological toxicity*			
	Haemoglobin	G3 = 0	G3 = 0	
	Leucocyte	G3 = 0	G3 = 5	
	Non-haematological toxicity			
	Late:			
	Lung	G3 = 0	G3 = 0	
	Oesophagus	G3 = 0	G3 = 0	
	Acute:			
	Lung	G3 = 0	G3 = 0	
	Oesophagus	G3 = 0	G3 = 8	
	Toxic deaths (*n*)	NR	NR	
Nyman 2009[58]	Haematological toxicity	NR	NR	
	Non-haematological toxicity			
	Oesophagitis	G3–4 = 20	G3–4 = 8	G3–4 = 19
	Pneumonitis	G3–4 = 0	G3–4 = 3	G3–4 = 3
	Toxic deaths (*n*)	NR	NR	NR
Zhu 2009[60]	Haematological toxicity	NR	NR	
	Non-haematological toxicity	NR	NR	
	Toxic deaths (*n*)	NR	NR	
Movsas 2010[61]	*Haematological toxicity*			
	Anaemia	G3–4 = 3	G3–4 = 19	
	Febrile neutropenia	G3–4 = 0	G3–4 = 6	
	Neutropenia	G3–4 = 28	G3–4 = 56	
	Thrombocytopenia	G3–4 = 6	G3–4 = 19	
	Non-haematological toxicity			
	Fatigue	G3–4 = 6	G3–4 = 16	
	Pneumonia	G3–4 = 3	G3–4 = 6	
	Radiation pneumonitis	G3–4 = 3	G3–4 = 0	
	Dyspnoea	G3–4 = 3	G3–4 = 9	
	Hypotension	G3–4 = 0	G3–4 = 6	
	Toxic deaths (*n*)	0	1	

NR, not reported.

Appendix 12 Protocol

CLINICAL AND COST EFFECTIVENESS OF FIRST-LINE THERAPY FOR ADULTS WITH NON-SMALL CELL LUNG CANCER

PROTOCOL – FEBRUARY 2010

1. Title of project

Clinical and cost effectiveness of first-line therapy for adult patients with non-small cell lung cancer.

2. TAR team

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For details of expertise within the TAR team see section 8.

3. Plain English summary

Non-small cell lung cancer (NSCLC) is a disease that affects almost 40,000 people in the UK each year. The treatment of the disease is hampered by its late diagnosis and very poor response to therapy and subsequently poor patient survival. In 2005 the National Institute for Health and Clinical Excellence (NICE) conducted a technology appraisal that evaluated the effectiveness of a number of drug therapies used to treat the disease. Over the past three to four years NICE has individually appraised a number of new drug treatments and made recommendations for treatment. These treatments have not been examined as a group or compared to each other. This proposal provides a protocol for a systematic review that will bring together the evidence related to the clinical effectiveness of these newer treatments, compared to those recommended in previous reviews as well as providing a re-examination of the cost effectiveness of the newer drug therapies.

4. Background

The most recent comprehensive review of chemotherapy treatment of NSCLC was conducted by Clegg *et al* in 2002[1] and was integral to the development of the NICE guidelines for the diagnosis and treatment of NSCLC in 2005.[2]

In 2005 the NICE Single Technology Appraisal (STA) process was introduced with the purpose of appraising technologies close to their date of launch to ensure the availability of appropriate technologies within the NHS as soon as possible. The design of the STA process means that each appraisal examines the use of a single technology for a single clinical indication. As a result, it is possible for several single technologies to be appraised for the same condition over a period of time with no formal link between the appraisals. NSCLC is an example of this and at least four STAs have been proposed or conducted regarding first-line chemotherapy treatments for patients with non-small cell lung cancer (NSCLC) since the inception of the STA process and since the previous comprehensive review of lung cancer treatments conducted by Clegg *et al* in 2002.[1] In fact the current NICE website lists a total of 13 appraisals that examine the treatment of NSCLC. These are a mix of first- and second- line treatment and comprise appraisals that are complete, have been terminated, delayed or are proposed.[3]

NICE is currently in the process of updating the guidelines related to the diagnosis and treatment of lung cancer.[4] LRiG has been in touch with the former head of the NICE clinical guidelines programme, Dr Fergus MacBeth, who has indicated that a comprehensive review of first-line therapy for NSCLC will not be undertaken as a part of this guideline process but that such a review would complement existing research in this area and that the availability of an up-to-date economic model would add great value. LRiG has contacted Andrew Champion (NCC manager) and Mia Schmidt-Hansen (systematic reviewer working on the update) who confirmed that the update will not include chemotherapy alone because there are so many NICE appraisals being done in the area. The guidelines group are however updating the review on chemoradiation. There are also indications that an updated Cochrane review is due to come out in mid-April 2010 which reviews chemoradiotherapy versus radiotherapy alone and also concurrent versus sequential chemoradiotherapy.

The Liverpool Reviews and Implementation Group (LRiG) has carried out a number of STAs in the area of NSCLC and believes that there is now a need to bring together the disparate clinical and cost effectiveness evidence for first-line treatment of NSCLC in the form of a comprehensive Health Technology Assessment report. We believe that an independent HTA report on chemotherapy and radical chemoradiotherapy for NSCLC will be very useful and will inform both current and future guidelines. This proposed review will assist policy makers in deciding how the newer NSCLC chemotherapy agents (e.g. pemetrexed) fit into the treatment pathway in the NHS in England and Wales.

This document describes the protocol for such a report and is being submitted for consideration as a part of LRiG's current TAR research contract. A decision was taken by LRiG regarding the importance of this project and therefore work on the clinical component of the project has already begun (see timelines below).

5. Decision problem

Background

Currently, NICE guidelines[2] recommend that chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status to improve survival, disease control and quality of life. This should consist of a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (carboplatin or cisplatin). Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation agent. NICE

also recommends that pemetrexed in combination with cisplatin may also be considered as a first-line therapy for patients with locally advanced or metastatic NSCLC who are confirmed as having large cell or adenocarcinoma histology. NICE has three other appraisals in its STA workplan.[5]

The current Scottish Intercollegiate Guidelines Network (SIGN) guideline states that chemotherapy with a platinum-based combination doublet regimen should be considered in all stage IIIB and IV NSCLC patients who are not suitable for curative resection or radical radiotherapy and are fit enough to receive chemotherapy. It further states that in these patients, the number of chemotherapy cycles given should not exceed four. No particular chemotherapy doublet or platinum agent is recommended in the guideline.[6]

The European Society for Medical Oncology (ESMO)[7] has published clinical recommendations for the diagnosis, treatment and follow-up of NSCLC. The recommendation for the treatment of stage IV disease states that 'Platinum-based combination chemotherapy prolongs survival, improves quality of life, and controls symptoms.' (p40)

Epidemiology

Lung cancer is the leading cause of death worldwide, while NSCLC accounts for approximately 80% of all lung cancers diagnosed.[8] The LUCADA database lists the main sub-types of NSCLC as squamous cell carcinoma (33%), adenocarcinoma (25%) and large cell carcinoma (4%), with the remaining 36% being NSCLC 'not-otherwise specified' (NSCLC-NOS).[9]

Over 38,000 people in the England and Wales were diagnosed with lung cancer in 2005 making it the second most commonly diagnosed cancer, after breast cancer, equivalent to more than 100 people per day being diagnosed with lung cancer. The link between smoking and lung cancer is well established: approximately 90% of lung cancer is the result of exposure to tobacco smoke. The link between smoking and poverty has also been proven; making lung cancer a disease that disproportionately affects people in the lowest socio-economic groups.[9,10] Survival from lung cancer is poor. Lung cancer was responsible for approximately 34,000 deaths in 2006 and is the most common cause of cancer death in the UK, accounting for more than one-in-five. Only 7% of lung cancer patients survive over five years after diagnosis.[10]

One reason for this poor prognosis is the late identification of the disease. Lung cancer is asymptomatic in the early stages – about two-thirds of patients are not diagnosed until it has reached advanced stages of the disease and is not amenable to curative treatment. Another reason, which explains the UK's relatively poor performance in comparison with other developed countries, is low active anti-cancer treatment rates.[10]

The technology

As outlined above there are several different first-line chemotherapy agents available to patients with NSCLC. In summary, chemotherapy treatments recommended by NICE include platinum-based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine; more recently, pemetrexed in combination with cisplatin has also been recommended by NICE for patients with large cell or adenocarcinoma.[2]

In addition, there are a variety of first-line chemotherapy treatments which have been approved by the European Medicines Agency (EMA) for patients with NSCLC that have not yet been appraised by NICE including gefitinib, cetuximab, bevacizumab and erlotinib.[3]

In addition, best supportive care (BSC) and different types of chemo-radiation are also first-line treatments that are available to patients with NSCLC. Current guidelines state that: 'Patients with stage III NSCLC who are not suitable for surgery but are eligible for radical radiotherapy should be offered sequential chemoradiotherapy.' (pg 8)[2]

Objectives of the HTA project

The objectives of the project are to evaluate the clinical and cost effectiveness of first-line therapy for adult patients with locally advanced or metastatic NSCLC.

6. Methods for synthesising clinical effectiveness evidence

Systematic review search strategy – published studies

The following databases will be searched for relevant published literature for the period 1990 to September 2009:

- EMBASE
- MEDLINE
- The Cochrane Library (which includes DARE, HTA and NHS EED)

Searches have been limited to these databases based on the evidence related to searching presented by Royle *et al*.[11] Details of the search strategies used to explore EMBASE and MEDLINE are available in *Appendix 1*. An update search will be carried out in 2010 to capture trials published during the production of this review.

Where electronic search facilities are available, the conference reports of organisations such as the American Society for Clinical Oncology (ASCO) will be searched for details of conferences and abstracts to identify any relevant studies and if data are available, these will be considered for inclusion in the review.

Bibliographies of previous reviews identified by the search (e.g. Clegg *et al* 2001[1]) and retrieved articles will be searched for further studies. The NICE website will be searched to identify manufacturers' submissions in this treatment area.

Clinical and statistical reviews of relevant chemotherapy treatments will be sought from the US Food and Drug Administration and the EMEA website will be examined to identify further trial information.

A database of relevant references will be developed using Endnote X3 software package.

Study selection

The citations identified by the search strategy will be assessed for inclusion through two stages. Firstly, two reviewers will independently screen all of relevant titles and abstracts identified via electronic searching to identify potentially relevant studies for inclusion in the review. Secondly, full text copies of these potentially relevant studies will be obtained and assessed independently by two reviewers using the inclusion and exclusion criteria outlined below (*Table 1*). Any disagreements between reviewers will be resolved by discussion at each stage and, if necessary, a third reviewer will be consulted.

Studies that do not meet all of the inclusion criteria will be excluded and their bibliographic details listed with reasons for exclusion. Ongoing studies that do not report relevant outcomes but meet the inclusion criteria will be listed for future use. In the event that data from randomised controlled trials (RCTs) are missing or limited, data from non-randomised studies may be used. The identification and use of such data will be described in the final report.

Inclusion criteria

TABLE 1 Inclusion criteria (clinical effectiveness)

Study design	Randomised controlled trials Systematic reviews of randomised controlled trials
Patient population	Chemotherapy naïve adult patients with locally advanced or metastatic non-small cell lung cancer
Interventions	Any first-line chemotherapy treatment currently licensed including: 1. Platinum-based chemotherapy (carboplatin or cisplatin) in combination with docetaxel, gemcitabine, paclitaxel, vinorelbine or bevacizumab 2. Pemetrexed plus cisplatin 3. Single agent therapies including erlotinib, gefitinib and cetuximab Any first-line chemo-radiation therapy
Comparators	It is envisaged that the interventions will be compared with 4. active therapy as described above or 5. best supportive care Comparisons of variation in dosing, timing (including concurrent or sequential) or mode of treatment regimens will also be included even when the intervention and comparator drug are the same
Outcomes	Primary outcomes: • Overall survival or • Progression free survival Secondary outcomes • Response rates • Adverse effects • Health related quality of life
Other considerations	Only studies published since 1990 in full and with English-language abstract will be included

Data extraction

Data from the included studies will be extracted as detailed below and will include the information listed in *Appendix 2*.

Data relating to population characteristics, study design and outcomes will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted on data extraction forms which will be piloted using a sample of included studies. Time permitting, authors and/or sponsors of the studies will be contacted for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all other relevant publications listed in the report.

Quality assessment

All included studies, will be assessed for methodological quality. The quality of RCTs will be assessed using criteria based on CRD Report No. 4[11] (see *Appendix 3*). Questions 4 and 5 will be adapted to reflect the characteristics of patients with NSCLC.

Data relating to quality assessment will be extracted by one reviewer and independently checked for accuracy by a second reviewer and any disagreements will be discussed; a third reviewer will be consulted, if necessary, to achieve consensus.

Methods of analysis/synthesis

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. The possible effects of study quality on the clinical effectiveness data and review findings

will be discussed. Where there are sufficient data, and it is appropriate to do so, meta-analyses will be performed using the Mantel–Haenszel methodology for a fixed-effect model. The meta-analysis will be carried out using the statistical package Review Manager 4.2. Treatment effects will be presented as weighted mean differences for continuous data.

Heterogeneity between trial results will be tested using a standard chi-squared test, with a threshold value of $p < 0.1$, and with the I^2 statistic.[12] Where quantitative heterogeneity is indicated, analysis using a random-effects model will be conducted for comparison with results of fixed-effect analysis to assess the robustness of the model chosen. The DerSimonian and Laird methodology will be used for the random effects model.[13] Heterogeneity between the included studies will be assessed by considering differences in (a) the study population (b) intervention (c) outcome measures and (d) study quality.

For binary outcomes (dichotomous data), where sufficient data are available, relative treatment effects will be presented in the form of odds ratios (OR) and/or relative risks (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used, the standardised mean difference (SMD) will be calculated provided skewness is not too great. For time to event outcomes, log hazard ratios (log HR) will be presented. Data will be pooled only if it is clinically and statistically relevant to do so.

Subgroup analyses will be conducted according to the type of disease (e.g. non-squamous, EGFR+ ect) and age of patients if suitable data are available.

7. Methods for synthesising cost effectiveness evidence

Systematic review of published economic literature

Search strategy

The search strategy described in section 6 will be used to identify studies examining the cost effectiveness of first-line chemotherapy for adult patients with NSCLC. The search strategy is designed to meet the primary objective of identifying economic evaluations for inclusion in the cost-effectiveness literature review. At the same time, the search strategy will be used to identify economic evaluations and other information sources which may include data that can be used to populate a de novo economic model where appropriate. Searching will be undertaken in MEDLINE and EMBASE as well as in the Cochrane Library, which includes the NHS Economic Evaluation Database (NHS EED). The dates for the searches will be from 1990 September 2009.

Study selection

Titles and abstracts will be examined for inclusion by two reviewers independently. Potentially relevant studies will then be obtained in full text and examined more carefully by two independent reviewers using the economic inclusion criteria outlined in *Table 2*. Any disagreement will be resolved by consensus, and if necessary a third reviewer will be consulted. Only full economic evaluations (assessing both outcomes and benefits) will be included. However, to supplement findings, additional information on costs and benefits will be collated and discussed in narrative format as appropriate.

Inclusion criteria

TABLE 2 Inclusion criteria (cost effectiveness)

Study design	Full economic evaluations that consider both costs and consequences (cost-effectiveness analysis, cost–utility analysis, cost–minimisation analysis and cost benefit analysis)
Outcomes	Incremental cost per life year gained Incremental cost per quality adjusted life year gained

Data extraction

Data from the full economic evaluations meeting the inclusion criteria will be extracted into structured tables and will include, but not be limited to, the criteria set out in *Appendix 4*[4]. Disagreement will be resolved through consensus and, if necessary, a third reviewer will be consulted. If time constraints allow, attempts will be made to contact authors for missing data. Data from multiple publications will be extracted and reported as a single study.

Quality assessment

The quality of the individual cost-effectiveness studies/models will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. The quality of the included studies will be assessed using the critical appraisal checklist for economic evaluations proposed by Drummond and colleagues[4] (see *Appendix 4*).This checklist reflects the criteria used to assess the quality of published economic evaluations as detailed in the methodological guidance developed by the NICE.[12] The information will be tabulated and summarised within the text of the report.

Methods of analysis/synthesis

(i) Cost-effectiveness review of published literature

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. Potential effects of study quality will be discussed.

(ii) Development of a de novo economic model

If appropriate data are available, an economic model will be developed to estimate the cost effectiveness of first-line chemotherapy treatments for patients with NSCLC. Where possible, the results will be presented as incremental cost per quality adjusted life year (QALY) ratios.

Methods for estimating costs, benefits and cost effectiveness ratios in the de novo economic model

a. Cost data

The primary perspective for the analysis of cost information will be the NHS and personal social services (PSS). Cost data will therefore focus on the marginal direct health service costs associated with the interventions. If evidence indicates that a societal perspective is required to credibly value all important costs and outcomes, this will be explored and presented in the sensitivity analysis. The relevant time horizon of analysis will be a patient's lifetime in order to reflect the chronic nature of the disease.

Quantities of resources used will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. Unit cost data will be extracted from the literature (e.g. Personal Social Services Research Unit) or obtained from other relevant sources (drug price lists, NHS reference costs and Chartered Institute of Public Finance and Accounting cost databases).

Where appropriate costs will be discounted at 3.5% per annum, the rate recommended in NICE guidance to manufacturers and sponsors of submissions.[12]

b. Assessment of benefits

A balance sheet will be constructed to list benefits and costs arising from alternative treatment options. LRiG anticipates that the main measures of benefit will be increased QALYs.

Where appropriate, effectiveness and other measures of benefit will be discounted at 3.5%, the rate recommended in NICE guidance to manufacturers and sponsors of submissions.[12]

c. Modelling

LRiG's ability to construct an economic model will depend on the data available. Where modelling is appropriate, a summary description of the model and a critical appraisal of key structures, assumptions, resources, data and sensitivity analysis (see Section d below) will be presented. In addition, LRiG will provide an assessment of the model's strengths and weaknesses and discuss the implications of using different assumptions in the model. The time horizon will be a patient's lifetime. Both costs and QALYs will be discounted at 3.5% as recommended by NICE.[12]

A formal combination of costs and benefits will also be performed, although the type of economic evaluation will only be chosen in light of the variations in outcome identified from the clinical-effectiveness review evidence.

If data are available, the results will be presented as incremental cost per QALY ratios for each alternative considered. If sufficient data are not available to construct these measures with reasonable precision, incremental cost-effectiveness analysis or cost–minimisation analysis will be undertaken.

d. Sensitivity analysis

If appropriate, sensitivity analysis will be applied to LRiG's model in order to assess the robustness of the results to realistic variations in the levels of the underlying parameter values and key assumptions. Where the overall results are sensitive to a particular variable, the sensitivity analysis will explore the exact nature of the impact of variations.

Imprecision in the principal model cost-effectiveness results with respect to key parameter values will be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question and to the potential impact on decision making for specific comparisons (e.g. multi-way sensitivity analysis, cost-effectiveness acceptability curves etc).

If evidence indicates that a societal perspective is required to value credibly all important costs and outcomes, this will be explored and presented.

8. Expertise in this TAR team

The Liverpool Reviews and Implementation Group (LRiG) was established at the University of Liverpool in April 2001. It is a multi-disciplinary research group whose purpose, in the first instance is to conduct Technology Assessment Reviews commissioned by the HTA programme. The team has substantial expertise in systematic reviewing, literature searching, assessing clinical outcomes, economic modelling and health economics, and is well practised in applying this expertise to health technology evaluations. In addition, various members of the team have been involved in recent STA appraisals in the area of NSCLC.

A subset of the LRiG team and local clinicians* have been selected on the basis of the specific expertise they bring to the project to work on this project (*Table 3*).

TABLE 3 LRiG team and expertise

Team member	Expertise	Contribution
Professor Adrian Bagust	Senior economic modeller	Economic modelling
Angela Boland	Health economics and systematic reviewing	Systematic review of economic evaluation/economic modelling
Tamara Brown	Systematic reviewing	Lead reviewer responsible for project management and systematic review of the clinical effectiveness data including meta-analyses
Ms Rumona Dickson Director of LRiG	Assessing clinical outcomes, systematic reviewing	Input into all aspects of the clinical component of the review
Yenal Dundar	Information specialist, assessing clinical outcomes	Development of the search strategies and input into the clinical components of the review
Emer McKenna*	Clinical/oncology expertise	Data extraction of clinical effectiveness data and input into clinical component of the review
James Oyee	Medical statistician	Assessment of medical statistics
Libby Richards*	Clinical/cancer treatment expertise	Data extraction of clinical effectiveness data and input into clinical component of the review
Carlos Saborido-Martin	Economic modelling	Economic modelling

9. Timetable/milestones

The previous involvement of the LRiG team in the appraisal of a variety of treatments for NSCLC within the STA process brought the LRiG team to the conclusion that there was a need for a full systematic review in this area. LRiG therefore identified local clinicians that were interested in the project and began work on the clinical component of this review during periods when other NICE projects were put on hold or cancelled. Work on this review has therefore begun but has been slow to move forward as other NICE and HTA work took priority. We are now proposing that this work be incorporated into our contracted TAR units for this and the coming year. Timelines for progression of the project are dependent on reviewer feedback and a decision regarding the appropriateness of including the work within our contract. Dates for completion therefore will be negotiated when these other decisions are taken.

Dates (estimated)	Activity
Internally done in January, 2009	Finalisation of protocol
Initial screening began in February, 2009	Screening of titles and abstracts
Completed January 2010	Inclusion/exclusion of full text papers
Commenced July 2009	Data extraction (clinical)
Commenced July 2009	Quality assessment (clinical)
TBC – not yet commenced	Data extraction (cost effectiveness)
TBC – not yet commenced	Quality assessment (cost effectiveness)
TBC – not yet commenced	Data synthesis and economic modelling
TBC	Draft report available for internal peer review
Depending on final HTA approval Provisionally December 2010	Full report submitted

10. Potential peer reviewers

Dr Noelle O'Rourke (Consultant Clinical Oncologist)
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11. References

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12. Appendices

Appendix 1 Details of clinical search strategies

Ovid MEDLINE(R) 1990 to March Week 3 2009

		Results
1	randomized controlled trial.pt.	266601
2	controlled clinical trial.pt.	78726
3	randomized.ab.	177144
4	placebo.ab.	110573
5	randomly.ab.	128581
6	trial.ab.	184266
7	or/1–6	579686
8	(animals not (humans and animals)).sh.	3254838
9	7 not 8	525513
10	exp Carcinoma, Non-Small-Cell Lung/ or nsclc.ti,ab.	18909
11	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.	18385
12	10 or 11	22812
13	exp Antineoplastic Combined Chemotherapy Protocols/ or *Combined Modality Therapy/ or exp chemotherapy, adjuvant/ or exp Radiotherapy/	182017
14	(chemotherap$ or radiotherap$ or chemo-radiation or chemoradiation or support$ care$ or palliat$ care$).ti,ab.	254221
15	(vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab).ab.	20673
16	or/13–15	355832
17	9 and 12 and 16	3045
18	limit 17 to (english language and yr="1990 – 2009")	2594

EMBASE 1990 to 2009 Week 13

		Results
1	Randomized Controlled Trial/	167319
2	randomized.ab.	171365
3	placebo.ab.	106176
4	randomly.ab.	114323
5	trial.ab.	168003
6	controlled clinical trial.pt.	0
7	Controlled Clinical Trial/	58798
8	or/1–7	464615
9	limit 8 to human	396769
10	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.	18740
11	exp Lung non Small Cell Cancer/ or nsclc.ti,ab.	22601
12	10 or 11	25216
13	Vindesine/ or Docetaxel/ or Cisplatin/ or Etoposide/ or Paclitaxel/ or Carboplatin/ or Navelbine/	128596
14	(chemotherap$ or radiotherap$ or chemo-radiation or chemoradiation or support$ care$ or palliat$ care$).ti,ab.	220301
15	(vinorelbine or paclitaxel or docetaxel or gemcitabine or pemetrexed or gefitinib or cetuximab or bevacizumab).ab.	20371
16	exp Cancer Radiotherapy/ or exp Chemotherapy/	225579
17	or/13–16	386860
18	9 and 12 and 17	3521
19	limit 18 to (english language and yr="1990 – 2009")	3034

Appendix 2 Details of clinical data extraction

Data extraction will include but may not be limited to:

Study details

- Author/Year/Endnote reference
- Randomisation
- Recruitment
- Funding
- Country
- Power
- Setting
- Population
- Inclusion/exclusion criteria (summary of trial inclusion/exclusion criteria)
- Intention to treat analysis done?
- Length of follow-up.

Intervention details

- Intervention (i.e. drug name(s) and details)
- Dose of intervention
- Duration of intervention.

Participant characteristics

- Number of participants randomised
- Number of participants assessed for primary outcome
- Age
- Sex
- Performance status
- Disease stage
- Were baseline demographics and disease state comparable?

Outcomes

- Overall survival
- Median survival time
- Survival rate
- Progression free survival
- Tumour response rate
- Duration of response
- Quality of life
- Haematological toxicity
- Non-haematological toxicity
- Toxic death.

Appendix 3 Details of clinical quality assessment

The quality of RCTs will be assessed using criteria based on CRD Report No. 4[13]

1. Was the method used to assign participants to the treatment groups really random?*
2. Was the allocation of treatment concealed?**
3. Was the number of participants who were randomised stated?
4. Were details of baseline comparability presented in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
5. Was baseline comparability achieved in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
6. Were the eligibility criteria for study entry specified?
7. Were any co-interventions identified that may influence the outcomes for each group?
8. Were the outcome assessors blinded to the treatment allocation?
9. Were the individuals who administered the intervention blinded to the treatment allocation?
10. Were the participants who received the intervention blinded to the treatment allocation?
11. Was the success of the blinding procedure assessed?
12. Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
13. Were the reasons for withdrawals stated?
14. Is there any evidence to suggest that the authors measured more outcomes than they reported?
15. Was an intention to treat analysis included?

*(Computer generated random numbers and random number tables will be accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates and days of the week)

** (Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially-numbered identical containers, on-site computer based systems where the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque).

Items will be graded in terms of ✓ yes (item properly addressed), ✗ no (item not properly addressed), ✓/✗ partially (item partially addressed), **?** unclear or not enough information, or NA not applicable.

Appendix 4 Details of economic data extraction and quality assessment

Cost effectiveness data extraction will include, but not be limited to:

- Type of evaluation and synthesis
- Intervention
- Study population/disease
- Time period of study
- Cost items
- Cost data sources
- Country, currency year
- Range of outcomes
- Efficiency data sources
- Modelling method and data sources
- Probabilities and assumptions of models
- Cost effectiveness ratios

- Subgroup analysis and results
- Sensitivity analysis and results
- Authors' conclusions.

Studies of cost effectiveness will be assessed for quality using the following criteria, which is an updated version of the checklist developed by Drummond:[4]

- Study question
- Selection of alternatives
- Form of evaluation
- Effectiveness data
- Costs
- Benefit measurement and valuation
- Decision modelling
- Discounting
- Allowance for uncertainty
- Presentation and generalisability of results.

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HTA
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PHR

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