

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

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Executive summary

Chemoradiation for adult patients with locally advanced non-small cell lung cancer

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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.

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