Survveillance report 2016 – Lung cancer (2011) NICE guideline CG121

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Surveillance decision

We will plan an update of the following sections of the guideline:

- Diagnosis and staging.
- Effectiveness of chemotherapy and radiotherapy for treatment of non-small-cell lung cancer (NSCLC).
- First-line treatment of limited-stage disease small-cell lung cancer (SCLC).
- First-line treatment for extensive-stage disease SCLC.

An extension to the scope will be needed to incorporate targeted therapies.

Reason for the decision

We found 320 new studies through surveillance of this guideline. New evidence that could affect recommendations was identified.

Topic experts advised us about whether the following sections of the guideline should be updated and any new sections added:

Diagnosis and staging

- What clinical factors and information from sequential tests determine the choice of next test for diagnosis and/or staging?

The evidence identified at the 4 year review on endobronchial ultrasound (EBUS) has a potential impact on NICE CG121, which advises offering EBUS-guided transbronchial needle aspiration (TBNA), or endoscopic ultrasound (EUS) guided fine needle aspiration (FNA), or non-ultrasound-guided TBNA as the first test for patients with an intermediate probability of mediastinal malignancy. It also advises that combined EBUS and EUS should be considered for initial staging of the mediastinum as an alternative to surgical staging. Topic experts agreed that the recommendation may require stronger wording in the light of the new evidence.

NICE CG121 assessed cost effectiveness on the basis of non-randomised controlled trial (RCT) data and modelling was used to calculate indicative costs. Topic experts agreed that health economic data from the ASTER study provides RCT evidence to inform an update of the health economic model in the guideline.
Curative treatment options for patients with NSCLC

- Effectiveness of surgery for treatment of NSCLC

The new systematic review evidence on video assisted thoracoscopic surgery (VATS) lobectomy for stage 1 NSCLC indicates that VATS may be superior to thoracotomy in terms of 5 year survival, recurrence, intra-operative blood loss, chest drainage time, hospital stay and complication incidence. However, thoracotomy may be superior in terms of lymph node sampling.

NICE CG121 does not make recommendations on the use of VATS as a minimally invasive technique for lobectomy, and there is therefore a potential need for a new recommendation in this area. Topic expert feedback indicated that there is sufficient existing evidence to form a recommendation. However, additional topic expert feedback indicated that further research, including the results of the ongoing VIOLET study, may be required to inform this and that publishing a recommendation on the basis of current evidence could potentially prevent recruitment to this trial.

Decision: The review question should be considered for a future update, following publication of the VIOLET study. This study is in the recruiting stage and updating the question now could potentially impact on the recruitment process. The surveillance team will track the findings of the VIOLET study.

- Chemotherapy for NSCLC: Which NSCLC patients are eligible for chemotherapy?

Topic expert feedback indicated that there is extensive literature building on prognostic and predictive biomarkers. It was considered an emerging area, but with insufficient evidence to result in new recommendations at this time. Further topic expert feedback emphasised the need for recommendations on epidermal growth factor receptor (EGFR) mutation status testing. These are already available through the related guidance EGFR-TK mutation testing in adults with locally advanced or metastatic NSCLC (2013) NICE diagnostics guidance DG9.

Decision: This review question should not be updated.

- Chemotherapy for NSCLC: Effectiveness of chemotherapy as treatment for NSCLC.

Topic expert feedback indicated that:
The 2011 update of the guideline did not include chemotherapy for NSCLC due to uncertainty about the results of multiple technology appraisals. A section on chemotherapy for NSCLC would make the guideline more complete.

- New combination therapies have emerged.

- Generic versions of gemcitabine and vinorelbine are available following UK patent expiry. An update to this section of the guideline would potentially need to encompass health economic modelling.

The new evidence suggests that gemcitabine plus paclitaxel may have similar efficacy to, and lower toxicity than, combination chemotherapy including a platinum-based drug. This was considered to have a potential impact on NICE CG121 for patients who are unable to tolerate platinum-based combination chemotherapy. Further new evidence indicated that docetaxel-based doublet therapy may be superior to docetaxel monotherapy as a second-line treatment for advanced NSCLC. This has a potential impact on NICE CG121, which states that docetaxel monotherapy should be considered if second-line treatment is appropriate.

The collective evidence and clinical feedback indicates that the review question should be updated, potentially to encompass health economic modelling.

**Decision:** This review question should be updated.

- Radiotherapy with curative intent for NSCLC: Effectiveness of radiotherapy as treatment for NSCLC.

Topic expert feedback confirmed that the NHS Commissioning Board is routinely commissioning Stereotactic Ablative Body Radiotherapy (SABR) for the subset of patients with early stage, inoperable NSCLC, and it is now routinely used for this indication, as set out in the NHS Commissioning Board's Clinical commissioning policy: stereotactic ablative body radiotherapy for non-small-cell lung cancer (adult). It was therefore considered necessary for NICE CG121 to be updated to reflect this.

Further clinical feedback indicated that patient travel and planning costs may be offset by delivering SABR in fewer factions and availability of equipment. Cost was not therefore considered to impede access to SABR.

The collective evidence, clinical feedback and NHS commissioning policy indicate that the recommendations may require updating, to incorporate the use of SABR in inoperable early stage NSCLC and its optimum dosing regimens.
Decision: This review question should be updated.

Treatment of SCLC: First-line treatment for limited-stage disease SCLC

- What is the most effective first-line treatment for patients with limited disease SCLC?

New systematic review and RCT evidence indicates that thoracic radiotherapy starting in the third cycle of chemotherapy, or after the first 30 days, is non-inferior to early thoracic radiotherapy in terms of the complete response rate, overall survival and progression free survival, and had a more favourable adverse effect profile. There is a potential impact on NICE CG121 to change to offering radiotherapy in the 3rd cycle or after 30 days to reduce adverse effects. Topic expert feedback indicated that in current clinical practice, thoracic radiotherapy is usually started in the second cycle of chemotherapy for patients with limited disease SCLC. Further topic expert feedback indicated that the timing of starting thoracic radiotherapy may not be as significant as the evidence suggests.

Topic expert feedback indicated that it would be sensible to await the results of the CONVERT trial, which is evaluating once vs twice daily radiotherapy, to update this related aspect of dosing regimen.

Decision: This review question should be updated, potentially following publication of the results of the CONVERT trial. Both the timing of starting thoracic radiotherapy and its daily dosing schedule should be considered. The surveillance team will track the findings of the CONVERT trial.

Treatment of SCLC: First-line treatment for extensive-stage disease SCLC

- What is the most effective regimen of chemotherapy for patients with extensive stage disease SCLC?

Topic expert feedback highlighted new evidence on palliative consolidation thoracic radiotherapy. The new RCT evidence by Slotman et al. (2015) suggests that thoracic radiotherapy following any response to four to six cycles of standard chemotherapy may improve survival outcomes. There is therefore a potential impact on NICE CG121, to extend thoracic radiotherapy to patients with any response to chemotherapy.

Topic expert feedback indicated that this is a very important area and good radiotherapy probably improves both symptoms and intermediate survival rates, so should be considered for inclusion in an update. Topic expert feedback further stated that the RCT provides good evidence and oncologists are already adopting this approach. However, additional topic expert feedback raised...
concern over the emphasis placed on this single RCT. It was therefore felt that the evidence base in this area should be re-examined.

**Decision:** This review question should be updated.

**Targeted therapies for NSCLC**

- New question – What is the effectiveness of targeted therapies for NSCLC?

There are no recommendations in the guideline on new cytotoxic or biologically targeted agents, which were either not licensed for use in the UK during development of NICE CG121 or were undergoing NICE technology appraisals. Topic experts agreed that there is a need to establish a new area in the guideline to incorporate or cross refer to relevant technology appraisals.

**Decision:** This review question should be included.

**Other clinical areas**

We also found new evidence that was not thought to have an effect on current recommendations. This evidence related to:

- Access to services and referral.
- Communication.
- Organisational factors relevant to diagnosis and staging.
- Combination treatment for patients with NSCLC.
- Maintenance treatment for SCLC.
- Effectiveness of chemotherapy for SCLC.
- Providing palliative care.
- Palliative radiotherapy for symptoms such as breathlessness due to endobronchial obstruction or vascular obstruction, persistent cough, haemoptysis and chest pain).
- Managing endobronchial obstruction.
- Managing other symptoms including weight loss, loss of appetite, difficulty swallowing, fatigue and depression.
We did not find any new evidence related to:

- Referral and indications for chest radiography.
- Impact of pre-operative smoking cessation/pre-operative pulmonary rehabilitation on outcomes following lung cancer surgery.
- The ability of exercise tests, lung function tests and/or global/other risk scores to predict post-operative morbidity and mortality in patients with resectable lung cancer.
- Eligibility of NSCLC patients for radiotherapy.
- Assessing patients with SCLC.
- Effectiveness of surgical treatment for patients with SCLC.
- Suitability of patients with SCLC for second line treatment.
- Other palliative treatments.
- Follow-up and patient perspectives.

For any new evidence relating to published or ongoing NICE technology appraisals, the guideline surveillance review deferred to the technology appraisal decision.

**Overall decision**

After considering all the new evidence and views of topic experts, we decided that a partial update with modified scope is necessary for this guideline.

See [how we made the decision](#) for further information.
Commentary on selected new evidence

With advice from topic experts we selected 3 studies for further commentary.

**Diagnosis and staging – endobronchial ultrasound**

We selected the health economics analysis of the ASTER trial by Rintoul et al. (2013) for a full commentary because topic expert feedback stated that NICE guideline CG121 assessed cost effectiveness of EBUS on the basis of non-RCT data and modelling was used to estimate indicative costs. Health economic data from the ASTER study provides RCT evidence which, despite the small UK sample, may help to further inform the health economic model originally developed for the guideline.

What the guideline recommends

NICE CG121 recommends that EBUS-guided TBNA, EUS-FNA, or non-ultrasound-guided TBNA should be offered as the first test for patients with an intermediate probability of mediastinal malignancy. Intermediate probability is defined as lymph nodes between 10 and 20 mm maximum short axis on computerised tomography.

NICE CG121 also recommends that combined EBUS-TBNA and EUS-FNA should be considered for initial staging of the mediastinum as an alternative to surgical staging.

Methods

Rintoul et al (2013) conducted a cost effectiveness analysis of the ASTER study (Assessment of surgical staging versus endobronchial and endosonographic ultrasound in lung cancer: a randomised clinical trial). The results of the ASTER trial demonstrated that mediastinal staging was more accurate for patients with suspected NSCLC who were randomised to combined EBUS-TBNA and EUS-FNA, followed by surgical staging if endoscopy was negative, versus surgical staging alone. The outcomes of the ASTER trial were the sensitivity, diagnostic accuracy and negative predictive value of each diagnostic strategy for detection of mediastinal nodal (N2/N3) metastases. The reference standard was any positive diagnostic test or if nodal involvement was detected after thoracotomy. The primary economic outcome was cost-utility of the endosonography diagnostic strategy relative to surgical staging alone. This outcome was considered up to 6 months after randomisation, from a UK NHS perspective. The aim of the further cost effectiveness analysis by Rintoul et al (2013) was to compare additional outcomes of survival, quality of life, and country specific cost effectiveness of the two diagnostic strategies over 6 months following randomisation. The study reported results for UK, Belgium and the Netherlands separately.
Quality of life was measured using EuroQoL EQ-5D at baseline, end of staging (before thoracotomy) and at 2 and 6 months after randomisation for all UK patients. EQ-5D responses were converted to quality-adjusted life years (QALYs).

For the cost effectiveness analysis, costs were estimated from an NHS and personal social services perspective for the UK. Direct healthcare costs per patient were calculated from resource use data for EBUS/EUS, surgical staging, thoracotomy and other surgery, chemotherapy, radiotherapy, hospital and hospice stays. The data were collected prospectively after April 2008. Data from patients recruited before April 2008 was collated retrospectively from medical records.

Statistical analysis included:

- Survival analysis using Kaplan–Meier and log rank methods.
- Mean utilities estimated from multivariate linear models.
- Bayesian parametric modelling to estimate expected costs and QALYs over 6 months after randomisation under each diagnostic strategy.

Results

In total, 241 patients were randomised, 118 (49%) to surgical staging and 123 (51%) to endosonography. Mean age was 64.5 years (standard deviation 8.9). Only 28 (12%) of the patients were from the UK.

The clinical results, published previously, showed that:

- The sensitivity for detecting mediastinal nodal metastases was significantly higher in the endosonography group (94%, 95% confidence interval [CI] 85% to 98%) than for surgical staging alone (79%, 95% CI 66% to 88%) (p=0.02).
- There were significantly more unnecessary thoracotomies in the surgical staging group (21/118 [18%]) than in the endosonography group (9/123 [7%]) (p=0.02).

Survival

Within 6 months of randomisation there were 20 deaths (8%), but the difference between the groups was non-significant (9 [7%] in the endosonography group; 11 [9%] in the surgical staging group; log rank test p=0.57).
**Quality of life**

In total, 144 (60%) patients completed baseline EQ-5D questionnaires. Additionally, questionnaires were also completed:

- at the end of staging by 139 (97%) patients
- at 2 months by 132 (92%) patients and
- at 6 months by 124 (86%) of patients.

Throughout the 6-month period, there was no significant difference between the groups in terms of EQ-5D utilities. The overall mean increase in quality-adjusted survival due to endosonography staging was very similar across the three countries. The resulting overall increase in QALYs for endosonography compared with surgical staging alone was 0.015 QALYs (95% CI –0.023 to 0.052) over 6 months.

**Resource use**

Staging procedures and thoracotomy were the most expensive parts of the diagnostic strategy. There were variations between countries in terms of median length of stay after thoracotomy and proportion of patients who had additional treatment. However, additional treatments, such as chemotherapy, were reported to have less impact on the overall costs. Their average costs were similar between the surgery and endosonography groups. Cost estimates for surgical staging and thoracotomy were lower in the endosonography arm across all countries. The total savings outweighed the additional costs of endosonography.

**Cost effectiveness**

The endosonography strategy achieved a lower mean cost and greater mean QALYs across all countries. The cost savings were greatest in the UK. The cost effectiveness acceptability curve showed that, based on willingness to pay for one additional QALY, the probability of the endosonography strategy being more cost effective compared with surgical staging was 82% in the UK. However, the willingness to pay threshold was not reported for the UK.
Strengths and limitations

Strengths

- The study was relevant to the NICE CG121 scope and used the same cost effectiveness measures adopted by NICE. It is therefore applicable to the guideline, although the study did not specify as an inclusion criterion the NICE CG121 intermediate probability of mediastinal malignancy, defined as lymph nodes between 10 and 20 mm maximum short axis on CT.

- The study contributes to addressing a gap in the evidence base relating to cost effectiveness of mediastinal staging.

- The study is based on RCT data, although the original RCT has not undergone critical appraisal through this surveillance process.

Limitations

The main limitations of the study, largely acknowledged by the authors were:

- The small sample size within each country (UK n=28).

- Longer term survival was not included and 6 months could be too short a time horizon. However, the authors argued that there would be little benefit from a lifetime cost effectiveness model because the majority of the differences between the groups resulted from the diagnostic tests and the thoracotomies, both of which occur early after randomisation. After 6 months, survival, quality of life and resource were expected to be determined by the course of lung cancer, so that costs and effects would be unlikely to diverge further beyond this point.

- Variation in the management of individual patients resulting in imprecise measurement of cost effectiveness.

- The methods for assigning costs to clinical events and tests varied between countries, dependent on the best information available. The authors stated that this prevented meaningful combination of costs.

- The later start of the cost-effectiveness component of the study resulted in some missing EQ-5D questionnaires and resource use components.
Impact on guideline

The findings of the study suggest that endosonography delivers greater health outcomes at lower or equal cost to surgical staging, or alternatively, cost savings with equal health outcomes. The findings were also supported by topic expert feedback and additional RCTs from the 4 year surveillance review. However, confirmatory studies of cost effectiveness in larger cohorts appear to be needed. The findings nevertheless reinforce and enhance NICE CG121 recommendations, which were based on expert opinion at the time of development. The additional health economic evidence may need to be incorporated into an update to the guideline.

Surgery with curative intent for NSCLC – video assisted thoracoscopic surgery

We selected the systematic review of randomised and non-randomised studies by Zhang et al. (2013) for a full commentary on the basis of its large pooled sample size, its assessment of an emerging intervention and its potential impact on the guideline. Topic expert feedback also highlighted the emergence of minimally invasive surgery, including VATS, as an important area of impact on outcomes and cited ongoing research in this area (Video assisted thoracoscopic lobectomy versus conventional open lobectomy for lung cancer [VIOLET study]).

What the guideline recommends

NICE CG121 recommends that for patients with NSCLC who are medically fit and suitable for treatment with curative intent, lobectomy should be offered (either open or thoracoscopic) as the treatment of first choice. NICE CG121 does not make recommendations on the use of VATS as a minimally invasive technique for lobectomy.

Methods

The systematic review aimed to compare VATS lobectomy to thoracotomy lobectomy for patients with early-stage NSCLC. The outcomes assessed were total and mediastinal lymph node dissection (LND) or lymph node sampling (LNS), systemic recurrence rate, loco-regional recurrence rate and long term survival rate.

Studies were included if they compared VATS with thoracotomy and reported the outcomes of interest.

The following studies were excluded:

- Studies that enrolled greater than 20% non-lobectomy procedures.
- Studies that enrolled greater than 10% neoadjuvant therapies.
- Non-English language studies.
- Studies where no data could be extracted.

**Results**

In total, 21 studies were included covering 5389 patients. Overall, 2380 patients underwent VATS and 3009 patients underwent thoracotomy. The imbalance was due to the inclusion of non-randomised studies with higher proportions of patients undergoing thoracotomy. The quality of the studies was reportedly good according to the assessment scores of the Newcastle–Ottawa and Jadad scales, for non-randomised and randomised studies, respectively.

**The results for the main outcomes were:**

**LND and LNS**

- The mean difference of total LND or LNS numbers between the two groups was not significant (-0.63, 95% CI -0.47 to 0.21, p=0.14), based on seven studies (n=1352) with available data, without evidence of significant heterogeneity (p=0.10, I²=44%).

- The difference in mediastinal LND or LNS numbers between the two groups was also non-significant (-0.51, 95% CI -1.58 to 0.56, p=0.35). This result was based on 4 studies (n=1124) with available data, but there was significant heterogeneity (p=0.04, I²=65%).

**Recurrence rate**

- There were 10 studies (n=2394) with available data for loco-regional recurrence rates, 9 (n=1983) of which also covered systemic recurrence rates.

- Systemic recurrence rates were significantly lower in the VATS group (relative risk [RR] 0.61, 95% CI 0.48 to 0.78, P<0.01), without significant heterogeneity (p=0.67, I²=0%).

- Loco-regional recurrence rates were significantly lower in the VATS group (RR 0.66, 95% CI 0.46 to 0.95, p=0.03), without significant heterogeneity (p=0.46, I²=0%).

**Survival rate**

- There were 13 studies (n=3304) with available data.

- Survival rate was significantly higher (RR 1.09, 95% CI 1.03 to 1.15, P<0.01) in the VATS group.
The included studies were heterogeneous (P<0.01, I²=63%).

In a sensitivity analysis (n=2240) to exclude the four studies where the follow-up period was 3 or 4 years, the heterogeneity was non-significant (p=0.08, I²=44%). The final results remained significantly higher in the VATS group (RR 1.10, 95% CI 1.04 to 1.17, P<0.01).

Strengths and limitations

Strengths

- The review added to the limited evidence base on an emerging and potentially important intervention.

- The search included multiple electronic databases and follow up of reference lists.

- Data extraction appears to have been done with low risk of bias, involving two independent reviewers, and the quality of included studies was formally assessed. However, the quality assessment tools used were outdated.

Limitations

- Inappropriate pooling of non-randomised studies with randomised studies in the meta-analysis. There was no sensitivity analysis by study design to explore potential bias.

- Inappropriate pooling of studies in the face of unexplained heterogeneity for the outcome of mediastinal LND or LNS.

- English language and date restrictions.

- The use of outdated quality assessment tools.

- Potential publication bias as indicated by a funnel plot analysis.

- The exclusion of some studies from the meta-analysis due to missing data, and no reported attempts to obtain the missing data.

- The authors were unable to obtain lymph node station results from most studies. The station is the position of the lymph node and is significant in lung cancer staging.

- Most studies were from the USA or Japan and may not fully represent treatment in the UK.

- Selection bias may have been introduced due to the retrospective design of the majority of included studies.
Impact on guideline

The study indicated that VATS results in lower recurrence rates and higher survival rates than thoracotomy, with similar LN evaluation outcomes, although the methodological limitations cast serious doubt on this conclusion. Additional evidence identified in the surveillance review supported these findings, in addition to fewer complications of VATS, although some RCT evidence showed no difference in survival rates. NICE CG121 does not make recommendations on the use of VATS as a minimally invasive technique for lobectomy, and there may be a potential need for a new recommendation in this area. Further research, including the results of the ongoing VIOLET study, may be needed to inform this.

Treatment – thoracic radiotherapy in extensive-stage SCLC

We selected the RCT by Slotman et al. (2015) for a full commentary because there is limited evidence in the area of SCLC, the study was highlighted by topic expert feedback and its results have a potential impact on the guideline recommendations.

What the guideline recommends

NICE CG121 recommends that for patients with extensive-stage disease SCLC, thoracic radiotherapy should be considered after chemotherapy if there has been a complete response at distant sites and at least a good partial response within the thorax.

Methods

The study aimed to evaluate the role of thoracic radiotherapy in addition to prophylactic cranial irradiation (PCI) for patients with extensive stage SCLC who had responded to chemotherapy. The eligibility criteria were:

- Adults aged 18 years or older.
- World Health Organization (WHO) performance status 0–2.
- Extensive stage SCLC (defined as disease beyond the hemithorax, hilar, mediastinal, and supraclavicular nodes).
- Any response after 4 to 6 cycles of standard chemotherapy (platinum etoposide).
- Treatable thoracic treatment volume using acceptable radiation fields.
- A maximum of six weeks between chemotherapy and randomisation.
- No clinical evidence of brain, leptomeningeal, or pleural metastases.
- No previous radiotherapy to brain or thorax.
- Ability to comply with protocol and follow-up schedules.

Patients were randomly assigned to receive either thoracic radiotherapy (30 Gy in ten fractions) or no thoracic radiotherapy. All underwent PCI. Patients in both groups were followed up at 6 weeks and 12 weeks, then once every 3 months in the first year, then 6 monthly thereafter. The primary outcome was overall survival (OS) at 1 year in the intention-to-treat population. The authors also conducted a post-hoc analysis of OS at 18 months. The authors also stated that they planned to analyse median OS and OS at 2 years, although these survival outcomes were not reported in the original protocol (NTR1527). Secondary outcomes were progression (intrathoracic control), pattern of failure, progression-free survival (PFS) (median and at 6 months), and toxic effects. The authors did not report any details on how these secondary outcomes were defined or measured.

**Results**

In total, 498 patients were randomised. Baseline characteristics appeared well balanced for most variables. However, smoking status was not reported.

WHO performance scores were imbalanced between intervention and control groups. There were a higher proportion of patients in the intervention group (39%) with WHO performance score of 0 compared to the control group (28%). There were a lower proportion of patients in the intervention group with a performance score of 1 (49%) than in the control group (63%). Although the statistical significance of these differences was not reported, it is possible that they may have influenced the results.

The primary endpoint of OS at 1 year was not significantly different between groups (hazard ratio [HR] 0.84, 95% CI 0.69 to 1.01, p=0.066). However, in a secondary analysis, 2-year OS was significantly better in the thoracic radiotherapy group compared to control: 13% (95% CI 9 to 19) compared with 3% (95% CI 2 to 8, p=0.004), but no hazard ratio was reported for this outcome. Progression (intrathoracic control) was less likely in the thoracic radiotherapy group than in the control group (HR 0.73, 95% CI 0.61 to 0.87, p=0.001). At 6 months, PFS was 24% (95% CI 19 to 30) in the thoracic radiotherapy group compared with 20% (95% CI 16 to 26) in the control group (N.B. the results data were obtained from the full text, which differed from the data reported in the abstract for PFS in the control group. The statistical significance is therefore unclear).
The authors reported no severe toxic events. The most common toxic effects recorded in both groups were grade 3 fatigue and dyspnoea.

A secondary analysis by the authors showed that patients with persistent intrathoracic disease after chemotherapy had significant improvements in OS, progression-free survival, and risk of intrathoracic progression as a result of thoracic radiotherapy. These benefits were not observed in patients without residual intrathoracic disease.

**Strengths and limitations**

**Strengths**

- The trial was well conducted, with a multi-centre design, clear inclusion criteria, intention to treat analysis and low attrition.

- The study population was directly relevant to the SCLC patient population stipulated in NICE CG121 for PCI treatment. This stipulated patients with extensive-stage disease SCLC and WHO performance status 2 or less.

- The study supplements and enhances the limited evidence base in the topic area.

- An additional secondary analysis identified patients with persistent intrathoracic disease after chemotherapy as a possible sub-group for patient selection.

**Limitations**

- There was a discrepancy between the data reported in the abstract and the data reported in the full text relating to progression free survival.

- There was an imbalance of baseline WHO performance scores between intervention and control groups, which may have influenced outcomes.

- Patient reported outcomes were not included, particularly in terms of quality of life.

- The trial allowed treatments of disease progression at the discretion of the participating treatment centres, and these uncontrolled interventions (or their absence) could have affected reported disease survival. The authors’ concluding suggestion to consider the universal application of post-chemotherapy thoracic radiotherapy may therefore be inappropriate.

- The authors state that they had planned to look at OS at 2 years, but this is not mentioned in their protocol recorded in the Netherlands trial register (NTR1527).
There was no initial subset analysis to identify sub-groups of patients that may benefit from the intervention, although this was partially addressed in response to post-publication comments.

Impact on guideline

The new RCT evidence suggests that thoracic radiotherapy in addition to PCI may improve 2 year OS and 6 month progression free survival for patients with any response to chemotherapy. There is a potential impact on the NICE CG121, which recommends that thoracic radiotherapy should be considered after chemotherapy if there has been a complete response at distant sites and at least a good partial response within the thorax. An additional secondary analysis of the RCT identified patients with persistent intrathoracic disease after chemotherapy as a possible sub-group for patient selection.
How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 4 years after the publication of lung cancer (2011) NICE guideline CG121.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in Developing NICE guidelines: the manual.

New evidence

We found 298 new studies in a search for randomised controlled trials and systematic reviews published between 28 May 2012 and 8 June 2015.

Evidence identified in an Evidence Update from 2 years after publication of the guideline was also considered. This included 22 studies identified by a literature search.

From all sources, 320 studies were considered to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: decision matrix for summaries and references for all new evidence considered.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline.

Views of stakeholders

Stakeholders are consulted only if we decide not to update the guideline following checks at 4 and 8 years after publication. Because this was a 4-year surveillance review, and the decision was to update, we did not consult on the decision.

See ensuring that published guidelines are current and accurate in Developing NICE guidelines: the manual for more details on our consultation processes.
The NICE project team would like to thank the topic experts who participated in the surveillance process.