



Effective Health Care

Treatment of Stage III Non-Small Cell Lung Cancer

Results of Topic Selection Process & Next Steps

The nominator, the American College of Chest Physicians (CHEST), is interested in a new evidence review on treating stage III non-small cell lung cancer to inform the update of their 2013 guidelines. Due to limited program resources, the program is unable to develop a review at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Treatment of Stage III Non-small cell lung cancer

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary

- This nomination meets all selection criteria.
- We identified 3 systematic reviews and a best evidence review that addressed some, but not all, of the key questions of interest. An in-process Cochrane review on chemoradiotherapy versus surgery-based treatment for Stage IIIA NSCLC will cover two of the questions in this nomination.
- Ten completed studies and one in-process were identified on the remaining key questions, for a projected total of 41 studies. A new evidence review would be small.

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Background

Lung cancer is the second most common cancer and the leading cause of cancer death in the United States.¹ The lifetime risk of developing lung cancer is 6.4 percent.¹ Non-small cell lung cancer (NSCLC), which consists of a range of cancer histologies including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma, accounts for 84% of the total lung cancer prevalence.² Treatment for NSCLC depends on patient factors such as cancer histology, extent to which and location where the cancer has spread (i.e., stage), other signs and symptoms, and a patient's general health.³ Patients with stage III NSCLC cancer have a range of presentations, from stage IIIA where the cancer has spread into the lymph nodes to stage IIIB where the cancer has spread to the lymph nodes and other organs such as the heart, blood vessels, trachea, esophagus, sternum, and/or backbone.³ Combined platinum-based chemotherapy with radiation therapy (i.e., chemoradiation) is the standard treatment for patients with stage III NSCLC. However, questions remain as to the optimal sequencing of chemotherapy and radiotherapy (i.e., sequentially or concurrently); timing and benefit of additional chemotherapies or targeted radiotherapies; benefits of surgical resection of the primary tumor, lobes, or entire affected lung; and benefits of post-treatment staging and subsequent treatment.

Nominator and Stakeholder Engagement: The American College of Chest Physicians (CHEST) nominated the topic *0769 Treatment of Stage III Non-Small Cell Lung Cancer* on February 22, 2018. The nominator would use a new AHRQ systematic review to update their 2013 clinical practice guidelines on this topic. The authors consulted with a local topic expert and worked with the nominator to refine the PICO of interest. During the topic work-up, the authors sent the nominator the protocol for an in-process Cochrane review to determine whether this might meet their needs for KQ 1, 3, 4, 7, or 8. The nominator responded that the Cochrane review would meet their needs for KQ 3 and 4 if the review was completed in time for their guideline development process, but would not meet their needs for KQ 1, 7 or 8.

The final key questions for this nomination are:

1. What is the effectiveness of concurrent chemoradiation therapy compared to sequential chemo-radiation among
 - a) Unresectable pathologic stage IIIA or IIIB NSCLC patients with good performance status (ECOG 0-1)
 - b) Pathologic stage IIIA or IIb NSCLC patients with marginal performance status (ECOG 2)
2. In patients with a complete response after treatment for Stage IIIA or IIIB NSCLC treated with definitive chemoradiation, what is the effectiveness of prophylactic cranial radiotherapy?
3. In patients with stage III lung cancer diagnosed intraoperatively and completely resectable gross disease, what is the effectiveness of complete surgical resection followed by adjuvant chemotherapy compared to definitive chemo-radiation therapy without resection?
4. In patients with stage IIIA lung cancer diagnosed pre-operatively, what is the effectiveness of neoadjuvant chemoradiation therapy followed by surgical resection compared to definitive chemoradiation without resection?
5. In patients with stage III lung cancer diagnosed pre-operatively, and treated with neoadjuvant chemoradiation therapy, does repeat pathologic staging of the mediastinum, followed by surgery only if the mediastinal nodes are pathologically negative, compared to surgery regardless of the status of mediastinal lymph nodes improve outcomes?

6. In patients with potentially resectable stage III lung cancer diagnosed pre-operatively, and treated with neoadjuvant chemo-radiation therapy who undergo re-staging of the mediastinum, a) what is the accuracy and b) what is effect on patient outcomes of staging with EBUS compared to PET scan?

7. In patients with stage III lung cancer diagnosed intraoperatively, does additional adjuvant radiotherapy after complete resection compared to adjuvant chemotherapy alone improve patient outcomes?

8. In patients with pathologically confirmed stage IIIA NSCLC and good performance status (ECOG 0-1) treated with neoadjuvant chemoradiation therapy followed by surgical resection, does requiring pneumonectomy for complete resection compared to requiring only lobectomy affect patient outcomes?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes (PICOs) of interest (Table 1).

Table 1. Key Questions and PICOTS

Key Questions	<p>1. What is the effectiveness of concurrent chemoradiation therapy compared to sequential chemo-radiation among</p> <p>a) Unresectable pathologic stage IIIA or IIIB NSCLC patients with good performance status (ECOG 0-1)</p> <p>b) Pathologic stage IIIA or IIb NSCLC patients with marginal performance status (ECOG 2)</p>	<p>2. In patients with a complete response after treatment for Stage IIIA or IIIB NSCLC treated with definitive chemo-radiation, what is the effectiveness of prophylactic cranial radiotherapy?</p>	<p>3. In patients with stage III lung cancer diagnosed intraoperatively and completely resectable gross disease, what is the effectiveness of complete surgical resection followed by adjuvant chemotherapy compared to definitive chemo-radiation therapy without resection?</p>	<p>4. In patients with stage IIIA lung cancer diagnosed pre-operatively, what is the effectiveness of neoadjuvant chemo-radiation therapy followed by surgical resection compared to definitive chemo-radiation without resection?</p>	<p>5. In patients with stage III lung cancer diagnosed pre-operatively, and treated with neoadjuvant chemo-radiation therapy, does repeat pathologic staging of the mediastinum, followed by surgery only if the mediastinal nodes are pathologically negative, compared to surgery regardless of the status of mediastinal lymph nodes improve outcomes?</p>	<p>6. In patients with potentially resectable stage III lung cancer diagnosed pre-operatively, and treated with neoadjuvant chemo-radiation therapy who undergo re-staging of the mediastinum, a) what is the accuracy and b) what is effect on patient outcomes of staging with EBUS compared to PET scan?</p>	<p>7. In patients with stage III lung cancer diagnosed intraoperatively, does additional adjuvant radiotherapy after complete resection compared to adjuvant chemotherapy alone improve patient outcomes?</p>	<p>8. In patients with pathologically confirmed stage IIIA NSCLC and good performance status (ECOG 0-1) treated with neoadjuvant chemo-radiation therapy followed by surgical resection, does requiring pneumonectomy for complete resection compared to requiring only lobectomy affect patient outcomes?</p>
Population	<p>Patients with unresectable pathologic stage IIIA or IIIB NSCLC and good performance status (ECOG 0-1)</p>	<p>Patients with a complete response after treatment for Stage IIIA or IIIB NSCLC treated with definitive chemo-radiation</p>	<p>In patients with stage III lung cancer diagnosed intraoperatively and completely resectable gross disease</p>	<p>Patients with stage IIIA lung cancer diagnosed pre-operatively</p>	<p>Patients with stage III lung cancer diagnosed pre-operatively, and treated with neoadjuvant chemo-radiation therapy</p>	<p>Patients with potentially resectable stage III lung cancer diagnosed pre-operatively and treated with neoadjuvant chemo-radiation therapy who undergo re-staging of the mediastinum</p>	<p>Patients with stage III lung cancer diagnosed intraoperatively</p>	<p>Patients with pathologically confirmed stage IIIA NSCLC and good performance status (ECOG 0-1) treated with neoadjuvant chemo-radiation therapy followed by surgical resection</p>

Table 1. Key Questions and PICOS

Intervention	Concurrent chemo-radiation therapy	Prophylactic cranial radiotherapy after chemo-radiation	Complete surgical resection followed by adjuvant chemotherapy	Neoadjuvant chemo-radiation therapy followed by surgical resection	Repeat pathologic staging of the mediastinum, followed by surgery only if the mediastinal nodes are pathologically negative	Staging with EBUS, staging with PET	Additional adjuvant radiotherapy and chemotherapy after complete resection	Pneumonectomy for complete resection
Comparator	Sequential chemo-radiation therapy	Definitive chemo-radiation alone	Definitive chemo-radiation therapy without resection	Definitive chemo-radiation	Surgery regardless of the status of mediastinal lymph nodes	Compared to each other, tissue histological confirmation or long-term clinical follow-up	Adjuvant chemotherapy after complete resection	Lobectomy
Outcome	Mortality, quality of life, toxicity	Incidence of cranial metastasis, mortality, quality of life, toxicity	Mortality, quality of life, toxicity	Mortality, quality of life, toxicity	Mortality, quality of life, toxicity	Sensitivity and specificity of test, mortality, quality of life, toxicity	Mortality, local control, quality of life, toxicity	Peri-operative mortality (30-day mortality), quality of life, toxicity

Abbreviations: EBUS= Endobronchial Ultrasound Bronchoscopy; ECOG= scale used to measure patients' functionality; NSCLC=Non-small cell lung cancer; PET= Positron emission tomography

Methods

We assessed nomination 0769 *Treatment of Stage III Non-Small Cell Lung Cancer* for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria (Appendix A). Assessment of each criteria determined the need for evaluation of the next one.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed from April 2013 to April 2018.

Because a large number of articles (n=836) were identified, we reviewed a random sample of 200 titles and abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample.

See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

Compilation of Findings

We constructed a table with the selection criteria and our assessments (Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. Lung cancer is the second most common type of cancer and the leading cause of cancer death in the United States.¹ NSCLC accounts for 84%

of the total lung cancer prevalence.² Patients with stage III NSCLC are a heterogeneous population, due to differences in histology, where and to what extent the cancer has spread, and other clinical characteristics. The optimal treatment of patients is highly variable depending on these treatment subgroups and has evolved as better treatments become available.

Desirability of New Review/Duplication

A new evidence review would be partially duplicative of an existing or in-process product. We identified 1 in-process Cochrane review, 2 completed systematic reviews, and a completed best evidence review that addressed some, but not all, of the key questions of interest.

Two systematic reviews partially addressed KQ1. One 2015 review⁴ examined radical-intent hypofractionated radiotherapy (radiotherapy given in large doses over a short period of time) used concurrently or sequentially with chemotherapy in patients with locally advanced NSCLC. This review did not present information on patients' performance status, so it only partially addresses the nominator's question. Another 2016 review⁵ examined treatment-related deaths during concurrent chemoradiation versus non-concurrent chemoradiation for patients with locally advanced NSCLC. This review similarly lacked information on patients' performance status, and it focused on treatment-related death, rather than death from any cause.

One in-process Cochrane review⁶ on chemo-radiotherapy versus surgery-based treatment for Stage IIIA non-small cell lung cancer will address KQ3 and 4. This review will conduct a network meta-analysis that includes nodes of chemoradiotherapy alone, surgery + chemotherapy, and surgery + chemoradiotherapy, among others. The review will examine overall survival and adverse events as primary outcomes, disease-free survival, locoregional recurrence-free survival, distant recurrence-free survival, and health-related quality of life as secondary outcomes. The nominator stated that this review would meet their needs for these two key questions if it was published in time to be incorporated into their guideline development process.

One best evidence review addressed KQ7. This 2017 review searched for the best evidence to determine if the addition of radiation to adjuvant chemotherapy after resection improved outcomes for patients with NSCLC and mediastinal lymphadenopathy.⁷ Although the methods were not systematic enough to be considered duplicative, the review identified 6 studies on this topic that were published since 2013.

See Table 2, Duplication column.

Impact of a New Evidence Review

A new systematic review on the treatment of stage III NSCLC may have high impact. CHEST's 2013 recommendations⁸ on treatment of stage III NSCLC are based on varied evidence, from 1A (strong recommendation, high quality evidence) to 2C (weak recommendation, low quality evidence). Because oncological treatments change rapidly, and there were many 2013 recommendations based on moderate or low-quality evidence, a new evidence review summarizing recent evidence could be impactful.

Feasibility of a New Evidence Review

A new evidence review examining KQ 1, 2, 5, 6, 7 and 8 is feasible. Ten completed studies and one in-process study were identified, for a projected total of 41 studies. A new review would be small.

Key Question 1: Five published studies addressed KQ1⁹⁻¹³ however, only one⁹ of these studies reported results by performance status in the abstract, and it was for a combined group of patients who received either sequential or concurrent chemoradiation. One in-process prospective study will examine dose escalation of radiation in stage II or III NSCLC patients

receiving neoadjuvant or no chemotherapy vs. concurrent chemotherapy. Authors did not comment on whether they planned to analyze data by performance status.¹⁴

Key Question 2: No studies were identified.

Key Question 3: Not assessed.

Key Question 4: Not assessed.

Key Question 5: No studies were identified.

Key Question 6: Four published studies¹⁵⁻¹⁸ addressed this key question, all of which examined either PET or combined PET/CT for determining whether there was a tumor response to chemoradiation treatment.

Key Question 7: A national registry study¹⁹ from the Netherlands included 2 cohorts of patients who received either resection with adjuvant chemoradiation or resection with adjuvant chemotherapy.

Key Question 8: The same national registry study¹⁹ identified for KQ 7 also conducted an analysis of lobectomy vs. pneumectomy.

See Table 2, Feasibility column.

Table 2. Key Questions and Results for Duplication and Feasibility

Key Question	Duplication (03/2015-03/2018)	Feasibility (04/2013- 04/2018)
KQ 1. Concurrent vs. sequential chemoradiation for those with: a) Good performance status (ECOG 0-1) b) Marginal performance status (ECOG 2)	Total number of identified systematic reviews: 2 • Other: 2 ^{4,5}	<u>Size/scope of review</u> Relevant Studies Identified: 5 • 1 RCT, ⁹ 1 non-randomized trial, ¹⁰ 1 prospective cohort, ¹¹ 1 retrospective cohort ^{12,13} Projected Total: 20 <u>Clinicaltrials.gov</u> • Active: prospective cohort ¹⁴
KQ 2. Prophylactic cranial radiotherapy after chemoradiation	None identified.	None identified.
KQ 3. Complete surgical resection w/ adjuvant chemotherapy vs. chemoradiation therapy alone	Total number of identified systematic reviews: 1 • Cochrane: 1 ⁶	Not assessed.
KQ 4. Neoadjuvant chemoradiation w/ surgical resection vs. definitive chemoradiation	Total number of identified systematic reviews: 1 • Cochrane: 1 ⁶	Not assessed.

Key Question	Duplication (03/2015-03/2018)	Feasibility (04/2013- 04/2018)
KQ 5. Surgery only if mediastinal nodes are pathologically negative vs. surgery regardless of status	None identified.	None identified.
KQ 6. Accuracy and effect on outcomes of PET vs. EBUS in staging patients after neoadjuvant chemoradiation	None identified.	<u>Size/scope of review</u> Relevant Studies Identified: 4 <ul style="list-style-type: none"> • 4 prospective observational¹⁵⁻¹⁸ Projected Total: 16 <u>Clinicaltrials.gov</u> None identified
KQ 7. Adjuvant radiotherapy + chemotherapy + resection vs. chemotherapy + resection	Total number of identified systematic reviews: 1 <ul style="list-style-type: none"> • Best evidence review: 1⁷ 	<u>Size/scope of review</u> Relevant Studies Identified: 1 <ul style="list-style-type: none"> • 1 registry study¹⁹ Projected Total: 4 <u>Clinicaltrials.gov</u> None identified
KQ 8. Pneumectomy vs. lobectomy after neoadjuvant chemoradiation therapy	None identified.	<u>Size/scope of review</u> Relevant Studies Identified: 1 <ul style="list-style-type: none"> • 1 registry study¹⁹ Projected Total: 4 <u>Clinicaltrials.gov</u> None identified

Abbreviations: KQ=Key Question; RCT=Randomized Controlled Trial

Value

The potential for value is high given this topic exists in a clinical context that is amenable to evidence-based change and CHEST plans to use an evidence review to update their 2013 guidelines on the treatment of stage III NSCLC.

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would be partially duplicative of an in-process product. An in-process Cochrane review on chemoradiotherapy versus surgery-based treatment for Stage IIIA NSCLC will cover two of the questions in this nomination.
- Impact: A new systematic review has high impact potential. Patients with stage III NSCLC are particularly difficult to manage, due to heterogenous patient characteristics. CHEST's most recent guideline was from 2013, many recommendations were based on moderate or low-quality evidence, and oncological treatments change rapidly, indicating a new evidence review summarizing recent evidence could impact practice.
- Feasibility: A new review on KQ 1, 2, 5, 6, 7 and 8 is feasible. The review would likely be small and would only summarize evidence on KQ 1, 6, 7 and 8 as no studies were identified for KQ 2 or 5.
- Value: The potential for value is high. CHEST plans to use a new review to update their 2013 clinical practice guidelines on this topic.

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Appendix A. Selection Criteria Summary

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, the topic represents health care interventions available in the United States.
1b. Is the nomination a request for a systematic review?	Yes, this is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes, the focus is on the comparative effectiveness of different treatment strategies for Stage III non-small cell lung cancer (NSCLC).
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, the nomination is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, lung cancer is the second most common type of cancer and the leading cause of cancer death in the United States. ¹ NSCLC, which consists of a range of cancer histologies including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma, accounts for 84% of the total lung cancer prevalence. ²
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, due to the large prevalence and low survival rate, this topic is of high public interest.
2c. Represents important uncertainty for decision makers	Yes, patients with stage III NSCLC are a heterogeneous population, due to differences in histology, where and to what extent the cancer has spread, and other clinical characteristics. The optimal treatment of patients is highly variable depending on these treatment subgroups and has evolved as better treatments become available.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this topic incorporates issues around benefits and harms, including mortality, quality of life, and toxicity.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, this nomination represents high costs, both because of the high prevalence of NSCLC and the high cost associated with chemotherapy, radiation, and surgical treatments.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	<p>A new evidence review would be partly duplicative of an existing or in-process product. We identified 1 in-process Cochrane review, 2 completed systematic reviews, and a completed best evidence review that addressed some, but not all, of the key questions of interest.</p> <ul style="list-style-type: none"> • KQ 1: Two systematic reviews partially addressed KQ1. One 2015 review⁴ examined radical-intent hypofractionated radiotherapy (radiotherapy given in large doses over a short period of time) used concurrently or sequentially with chemotherapy in patients with locally advanced non-small cell lung

	<p>cancer. This review did not present information on patients' performance status, so it only partially addresses the nominator's question. Another 2016 review⁵ examined treatment-related deaths during concurrent chemoradiation versus non-concurrent chemoradiation for patients with locally advanced non-small cell lung cancer. This review similarly lacked information on patients' performance status, and it focused on treatment-related death, rather than death from any cause.</p> <ul style="list-style-type: none"> • KQ 3 and 4: One in-process Cochrane review⁶ on chemo-radiotherapy versus surgery-based treatment for Stage IIIA non-small cell lung cancer will address KQ3 and 4. This review will conduct a network meta-analysis that includes nodes of chemoradiotherapy alone, surgery + chemotherapy, and surgery + chemoradiotherapy, among others. The review will examine overall survival and adverse events as primary outcomes, disease-free survival, locoregional recurrence-free survival, distant recurrence-free survival, and health-related quality of life as secondary outcomes. The nominator stated that this review would address their needs for these two key questions. • KQ 7: One best evidence review addressed KQ7. This 2017 review searched for the best evidence to determine if the addition of radiation to adjuvant chemotherapy after resection improved outcomes for patients with NSCLC and mediastinal lymphadenopathy.⁷ Although the methods were not systematic enough to be considered duplicative, the review identified 6 studies on this topic that were published since 2013.
<p>4. Impact of a New Evidence Review</p>	
<p>4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?</p>	<p>The standard of care is unclear. CHEST's 2013 recommendations⁸ on treatment of stage III NSCLC are based on varied evidence, from 1A (strong recommendation, high quality evidence) to 2C (weak recommendation, low quality evidence). Because oncological treatments change rapidly, and there were many 2013 recommendations based on moderate or low-quality evidence, a new evidence review could be impactful.</p>
<p>4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?</p>	<p>Yes, there is practice variation, but it is mainly due to uncertainty surrounding which patients should receive which treatments.</p>
<p>5. Primary Research</p>	

<p>5. Effectively utilizes existing research and knowledge by considering:</p> <ul style="list-style-type: none"> - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies) 	<p><i>Size & scope of a review:</i> A new evidence review is feasible. We identified a total of 10 completed studies and 1 in-process study addressing the key questions, for a projected total of 41 studies. A review would be small.</p> <ul style="list-style-type: none"> • <u>KQ 1:</u> Five published studies addressed KQ1⁹⁻¹³ however, only one⁹ of these studies reported results by performance status in the abstract, and it was for a combined group of patients who received either sequential or concurrent chemoradiation. • <u>KQ 2:</u> No studies were identified. • <u>KQ 3:</u> Not assessed. • <u>KQ 4:</u> Not assessed. • <u>KQ 5:</u> No studies were identified. • <u>KQ 6:</u> Four published studies¹⁵⁻¹⁸ addressed this key question, all of which examined either PET or combined PET/CT for determining whether there was a tumor response to chemoradiation treatment. • <u>KQ 7:</u> A national registry study¹⁹ from the Netherlands included 2 cohorts of patients who received either resection with adjuvant chemoradiation or resection with adjuvant chemotherapy. • <u>KQ 8:</u> The same national registry study¹⁹ identified for KQ 7 also conducted an analysis of lobectomy vs. pneumectomy. <p><i>ClinicalTrials.gov.</i> One in-process study will potentially address key question 1.</p> <ul style="list-style-type: none"> • <u>KQ 1:</u> One in-process prospective study will examine dose escalation of radiation in stage II or III NSCLC patients receiving neoadjuvant or no chemotherapy vs. concurrent chemotherapy. Authors did not comment on whether they planned to analyze data by performance status.¹⁴
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, this topic exists in a clinical context that is amenable to evidence-based change.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, CHEST plans to use an evidence review to inform the update of their 2013 guidelines on treatment of stage III NSCLC.

Abbreviations: CHEST= American College of Chest Physicians; CT=Computed tomography; KQ=Key Question; NSCLC= Non-small cell lung cancer; PET= Positron emission tomography

Appendix B. Search for Evidence Reviews (Duplication)

Listed are the sources searched.

Search date: 03/2015 to 03/2018
AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PubMed
PubMed Health http://www.ncbi.nlm.nih.gov/pubmedhealth/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
CADTH (Canadian Agency for Drugs and Technologies in Health) https://www.cadth.ca/
DoPHER (Database of promoting health effectiveness reviews) http://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9
ECRI institute https://www.ecri.org/Pages/default.aspx
PsycINFO (Ovid)

Appendix C. Search Strategy & Results (Feasibility)

Treatment of Stage III Non-Small Cell Lung Cancer MEDLINE(PubMed) April 4th, 2018	
Concept	Search String
Non-Small Cell Lung Cancer	(((("Carcinoma, Non-Small-Cell Lung/drug therapy"[Mesh] OR "Carcinoma, Non-Small-Cell Lung/radiotherapy"[Mesh] OR "Carcinoma, Non-Small-Cell Lung/surgery"[Mesh] OR "Carcinoma, Non-Small-Cell Lung/therapy"[Mesh]))) OR (("non small cell lung"[Title/Abstract]) AND (cancer[Title/Abstract] OR carcinoma[Title/Abstract] OR neoplasm[Title/Abstract]))
AND	
Treatment	(((("Therapeutics"[Mesh] OR "therapy" [Subheading]) OR ("Drug Therapy"[Mesh] OR "drug therapy" [Subheading]))) OR ("radiotherapy" [Subheading] OR "Radiotherapy"[Mesh])) OR "surgery" [Subheading]
NOT Editorials, etc.	((((((letter[Publication Type]) OR news[Publication Type]) OR patient education handout[Publication Type]) OR comment[Publication Type]) OR editorial[Publication Type]) OR newspaper article[Publication Type]
Limit to last 5 years; human ; English ; Adult	Filters activated: published in the last 5 years, Humans, English, Adult: 19+ years
<i>Since the results were so large, in order to better find which KQ have evidence for them, the results for each KQ are presented here</i>	
KQ1 & 4 & 7: Chemo-radiation therapy	("Chemoradiotherapy"[Mesh]) OR ((chemoradiation[Title/Abstract] OR chemoradiotherapy[Title/Abstract]))
N=491 SRN=8 https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54683875/public/ RCTN=241 https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54683887/public/ OtherN=242 https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54683896/public/	

KQ2: Prophylactic cranial radiotherapy	("Cranial Irradiation"[Mesh]) OR ("Prophylactic cranial irradiation"[Title/Abstract]) OR "Prophylactic cranial radiotherapy"[Title/Abstract])
N=56 SR=1 https://www.ncbi.nlm.nih.gov/pubmed/?term=29365347 RCT=29 https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54683935/public/ Other=26 https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54683944/public/	
KQ3 & 4 & 7 & 8: Surgical resection	("Margins of Excision"[Mesh]) OR "Surgical resection"[Title/Abstract]
N=301 SR=7 https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54683970/public/ RCT=117 https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54683977/public/ Other=177 https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54683991/public/	
KQ5: Repeat Staging (in general)	((((((cancer[Title/Abstract] OR neoplasm[Title/Abstract] OR Carcinoma[Title/Abstract])) AND staging[Title/Abstract])) OR "Neoplasm Staging"[Mesh])) AND repeat[Title/Abstract]
N=15 SR=0 RCT=9 https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54684048/public/ Other=6 https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54684063/public/	
KQ6: Repeat Staging by EBUS OR PET Scan	((((((((cancer[Title/Abstract] OR neoplasm[Title/Abstract] OR Carcinoma[Title/Abstract])) AND staging[Title/Abstract])) OR "Neoplasm Staging"[Mesh])) OR (((("Endobronchial ultrasound"[Title/Abstract] OR EBUS-NA[Title/Abstract]) OR "Ultrasonography"[Mesh]))) AND repeat[Title/Abstract]
N=15 SR=0 RCT=9 https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54684090/public/ Other=6 https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/54684095/public/	

ClinicalTrials.gov searched on March 4th, 2018

47 Studies found for: *Completed Studies* | Non Small Cell Lung Cancer | radiotherapy OR chemotherapy OR surgery | Adult, Senior | Start date from 01/01/2013 to 12/31/2018

https://clinicaltrials.gov/ct2/results?cond=Non+Small+Cell+Lung+Cancer&term=&intr=radiotherapy+OR+chemotherapy+OR+surgery&strd_s=01%2F01%2F2013&strd_e=12%2F31%2F2018&cntry=&state=&city=&dist=&Search=Search&recrs=e&age=1&age=2

84 Studies found for: *Active, not recruiting Studies* | Non Small Cell Lung Cancer | radiotherapy OR chemotherapy OR surgery | Adult, Senior | Start date from 01/01/2013 to 12/31/2018

https://clinicaltrials.gov/ct2/results?cond=Non+Small+Cell+Lung+Cancer&term=&intr=radiotherapy+OR+chemotherapy+OR+surgery&strd_s=01%2F01%2F2013&strd_e=12%2F31%2F2018&cntry=&state=&city=&dist=&Search=Search&recrs=d&age=1&age=2