

Evidence-based Practice Center Systematic Review Protocol

Project Title: Local Therapies for the Treatment of Stage I Non-Small Cell Lung Cancer and Endobronchial Obstruction Due to Advanced Lung Tumors

I. Background and Objectives for the Systematic Review

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality worldwide, with over 1 million deaths per year.¹ In the United States, lung cancer is the leading cause of cancer death; in 2010, an estimated 222,520 cases were expected to be diagnosed, with 157,300 deaths due to the disease.¹

Stage I Non-small Cell Lung Cancer

Only about 20 percent of patients with NSCLC present with stage I (T1N0M0, T2N0M0) disease, which is localized and without nodal involvement. Surgical excision, either lobectomy or pneumonectomy, is the current definitive standard of care for eligible patients with stage-I NSCLC. After complete surgical resection, the 5-year overall survival is around 70 percent because of tumor recurrence, noncancer-related mortality, and second malignancies.^{2, 3}

Malignant Endobronchial Obstruction

About 20 to 30 percent of patients with NSCLC present with inoperable endobronchial obstruction from primary or recurrent stage IIIa, IIIb, or IV lung tumors, manifested by symptoms of disabling dyspnea, cough, and hemoptysis.^{4, 5} Up to 40 percent of lung cancer deaths may be attributed to such locoregional disease. Management of patients with advanced disease is a significant challenge. The ability to alleviate airway distress may be lifesaving, as some patients may present within hours of succumbing to suffocation.⁵⁻⁷

Treatment Indications

A subset of patients with stage-I NSCLC are deemed medically inoperable, primarily because of pre-existing diminished cardiac reserve, poor pulmonary function, and poor performance status.^{2, 3, 8, 9} Another subset of candidates for nonsurgical treatment options includes patients whose disease is deemed operable but decline surgery. The latter group of patients may indeed be healthier than those who are deemed medically inoperable and have different outcomes.

Patients with advanced (stage IIIa, IIIb, or IV) NSCLC often require emergency treatment to relieve airway obstruction or stop bleeding. While such treatment typically represents palliative therapy, it may be performed in some patients (e.g., stage IIIa) with curative intent.

Current Treatments

Surgical resection is the standard of care for stage-I NSCLC. Comparing interventional ablative and external beam radiotherapy (RT) procedures to surgery in this setting is difficult, as surgical candidates likely reflect a different, generally healthier patient group than patients whose tumors are medically inoperable. This comparison is outside the scope of the comparative effectiveness review (CER).

Nonsurgical Definitive Treatment Options for Stage I Non-small Cell Lung Cancer

Thoracic RT plays a pivotal role in the definitive treatment of patients with stage-I NSCLC who are deemed medically inoperable and in those who decline surgery.^{2, 3} Ideally, RT balances delivery of a cytotoxic dose of ionizing radiation to the tumor volume, while attempting to minimize adverse effects of radiation on adjacent normal lung tissue and thoracic structures. Several RT modalities have been used to treat patients with stage-I NSCLC, as follows.

Conventional Two-Dimensional External Beam Radiotherapy. Conventional two-dimensional external beam radiotherapy (2D-EBRT) consists of a single beam from one to four directions with the radiation fields designed based on 2D fluoroscopic simulation images. It encompasses the tumor and a significant margin of normal tissue to avoid missing any part of the tumor and to maximize the likelihood of a favorable therapeutic outcome. It involves numerous treatment sessions, with dose fractionation, and can lead to adverse effects related to the effect of radiation on normal lung tissue, including radiation pneumonitis and permanent loss of noncancerous lung tissue. While higher radiation doses enhance local tumor control, as a function of a dose-response relationship for both local control and survival, dose escalation with conventional EBRT is associated with dose-limiting toxicities, such as radiation fibrosis and pneumonitis. Poor local control with conventional EBRT is associated with inaccurate tumor targeting, failure to conform the dose distribution to the target volume, and an associated failure to deliver an adequate dose of radiation.⁸ Until recently, conventional EBRT was the standard of care for patients with inoperable stage-I NSCLC, offering a relatively poor chance of cure with long-term survival rates of 3 to 13 percent overall and perhaps 30 to 50 percent at 5 years in patients with T1 tumors.⁸

Conventional EBRT is of historical interest as a comparator for conformal RT techniques in patients with stage-I NSCLC, but it is no longer in routine use in modern radiation oncology practice in this setting. It will not be considered as a comparator in the stage I local treatment setting.

External Beam Conformal Radiotherapy Options. Inadequate survival outcomes with 2D-EBRT led to development and application of newer conformal RT methods, including 3-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and stereotactic body radiation therapy (SBRT) for definitive (curative) treatment of inoperable patients with stage-I NSCLC.¹⁰⁻¹²

3D-CRT employs computed tomographic (CT) simulation, allowing for more accurate dose calculations by taking into account axial anatomy and complex tissue contours. Three-dimensional anatomic information from diagnostic CT scans are used to deliver multiple (100–200) highly focused beams of radiation that converge at the tumor site.⁸ This approach allows

accurate and precise conformity of the radiation to the tumor volume, with very rapid dose fall-off in surrounding normal lung parenchyma.

IMRT, which has been implemented over the last decade, has further refined radiation dose delivery.^{11, 13, 14} IMRT permits the modulation of both the number of fields and the intensity of radiation within each field, allowing for greater control of the dose distribution to the target. A potential theoretical benefit of IMRT is the ability to deliver higher doses to the tumor than with other methods with greater tumoricidal effectiveness. However, while dose-histogram studies suggest IMRT allows better conformality of the high-dose volume to the tumor, questions continue about the relative benefits and harms of this technique, because IMRT actually increases the volume of lung that receives a low radiation dose and may actually increase the rate of injury.¹¹

SBRT delivers very high, conformal doses of radiation in fewer treatment sessions (generally 3–8 fractions), with the potential to cause less damage to surrounding normal tissue.¹⁵ While SBRT appears to be supplanting other conformal RT methods for definitive treatment of stage-I NSCLC, the relative balance of benefits and harms in this setting is unclear.

Proton beam radiotherapy (PBRT) represents another conformal RT option for stage-I NSCLC. PBRT delivers high doses of radiation to the tumor. Proton beams enter the body with a low radiation dose, stop at the tumor, match its shape and volume or depth, and deposit the bulk of their cytotoxic energy within the tumor; thus, this type of treatment may cause less damage to surrounding healthy tissue.¹⁶

The optimal definitive external RT modality is not defined for patients with medical contraindications (patients whose disease is medically inoperable) or for those with stage-I NSCLC who elect nonsurgical treatment.¹² SBRT is used in patients considered unfit for surgery, and some investigators suggest it could become the standard of care for this indication.¹⁷⁻²⁰ However, other conformal RT methods, including IMRT and 3D-CRT, have been used in this setting. All of these RT procedures are time-intensive, require significant training, and necessitate substantial advance planning.^{11, 14} Institutional quality-control processes are required to assure their safe and effective use, in particular IMRT.¹³ Analysis of the application of PBRT to NSCLC presents challenges secondary to the small number of institutions that have experience with this technique and small reported patient numbers.¹⁶

Interventional Treatment Options

Interventional treatment options for stage-I NSCLC include radiofrequency ablation (RFA).^{15, 21} Percutaneous RFA is a minimally invasive technique that uses high-frequency electric currents to heat and destroy a tumor and is typically performed in a single session with few adverse effects.²² The most frequent complication of RFA is pneumothorax.¹⁷ Analysis of the application of RFA to NSCLC presents challenges secondary to the small number of institutions that have experience with this technique and small numbers of reported patients.^{16, 22, 23}

Brachytherapy (BT) was used for definitive treatment of stage I nonsurgical patients, but is now considered appropriate only as an adjunct to surgery.²⁴ It will not be considered as a comparator in this setting in this CER.

Malignant Endobronchial Obstruction

Treatment Options for Malignant Endobronchial Obstruction

The choice of treatments is a function of tumor stage and the level of patient distress. Among patients with stage IIIa disease, treatment may be undertaken to relieve symptoms, to improve quality of life, and with curative intent. Among patients with stage IIIb or IV disease, improved quality of life and palliation are the primary treatment goals.

Conventional Two-Dimensional External Beam Radiotherapy (2D-EBRT). Patients with good performance status may benefit from higher dose, low-fraction external beam RT (EBRT) to relieve symptoms (e.g., hemoptysis, cough, chest pain, dyspnea, obstructive pneumonia, dysphagia, etc.) associated with endobronchial obstructive tumor.⁷

Interventional Options. Endobronchial BT is another option for endobronchial obstruction and can be used alone or with EBRT to boost the total dose of irradiation used.^{7, 25} It has been used in combination with high-dose EBRT as a potential curative primary treatment in selected cases (stage IIIa). Serious complications have been described with endobronchial BT, including massive hemoptysis, tracheoesophageal fistulas, bronchial stenosis, and radiation bronchitis.²⁵

The role of endobronchial BT for the palliative treatment of symptomatic patients with endobronchial obstruction is unclear. It has been used as a palliative treatment in case of endobronchial tumor recurrence after EBRT. Endobronchial BT also may be an option for patients in whom EBRT fails to relieve symptoms or for those with endobronchial disease who require lung re-expansion before or in conjunction with radical RT.⁷

Interventional bronchoscopy with mechanical debulking can re-establish airway patency in a large proportion of patients with malignant endobronchial obstruction due to advanced stage disease (IIIa, IIIb, or IV). This procedure relieves dyspnea effectively and rapidly, although results may not always translate into improvements in overall quality of life.⁶ Similarly, endobronchial stent placement can reduce respiratory distress in patients with malignant endobronchial obstruction.²⁶ This procedure may be safely performed in an outpatient setting with conscious sedation alone and with few complications such as stent migration.

Objectives

This CER of local therapies for stage I (T1N0M0, T2N0M0) NSCLC and endobronchial obstruction due to stage IIIa, IIIb, or IV lung tumors will provide a comprehensive analysis of the relative benefits and harms of lung-directed nonsurgical therapies in two disease settings encompassing four distinct patient populations (see PICOTS [Population, Intervention, Comparator, Outcome, Timing and Setting] framework below). These topics are clinically relevant and necessary because of uncertainty surrounding optimal use of the various local therapies in these settings and because of its importance to health care providers, patients, and policymakers.

Summary

Several local nonsurgical therapies are available for definitive treatment of inoperable stage-I NSCLC, including conformal radiation modalities (3D-CRT, IMRT, SBRT, PBRT), and

interventional methods such as RFA. Likewise, numerous methods are used to treat patients with symptomatic malignant endobronchial obstruction, including EBRT methods, BT, surgical debriement and stent placement, and others (e.g., YAG [yttrium-aluminum-garnet] laser, cryoablation).

Malignant endobronchial obstruction secondary to stage IIIa, IIIb, or IV NSCLC is a significant challenge. Treatment with curative intent may be undertaken for patients with stage IIIa disease, whereas those with stage IIIb or IV will be treated with palliative intent. In both groups, the ability to alleviate airway distress may be lifesaving, at least in the short term, as some patients may present within hours of succumbing to suffocation.⁵⁻⁷

II. The Key Questions

The Key Questions (KQs) were posted for public comment on the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program Web site for 4 weeks. Based on these comments and discussion with the Technical Expert Panel (TEP), changes were made to the KQs, the PICOTS, and analytical frameworks, as follow:

- KQ 2 originally was intended to consider patients who were deemed “technically inoperable” by virtue of having a tumor “>T2” or secondary to inaccessible location. Patients with >T2 tumors do not conform to the American Joint Committee on Cancer’s definition of stage-I NSCLC and thus are not candidates for the definitive local interventions that are the topic of this CER, so based on input from the TEP, this KQ was deleted from the original version of the protocol. KQs 1 and 2 will consider, respectively, adult (age 18 years or older) patients with documented (clinical or pathological) stage-I NSCLC for whom surgery is contraindicated secondary to comorbidities or those who are deemed operable but who decline surgery.
- For KQs 1 and 2, conventional 2D-RT and BT were deleted as interventions based on input from the TEP as these treatments are not currently used in this setting.
- For KQ 3, laser therapy (undefined) and cryoablation were added as potential interventions, whereas PBRT was removed as the TEP viewed it as inappropriate for patients with symptomatic, advanced stage cancer who are unlikely to tolerate the stresses associated with travel to a facility and the treatment itself.

Question 1

What are the comparative benefits and harms of local nonsurgical therapies for documented (clinical or biopsy) stage I (T1N0M0, T2N0M0) NSCLC in adult patients (age 18 years or older) who are not surgical candidates because of the presence of contraindications to major surgery, for example, cardiac insufficiency, poor pulmonary function, presence of severe intercurrent illness, or poor performance status?

Question 2



What are the comparative benefits and harms of local nonsurgical therapies for documented (clinical or biopsy) stage I (T1N0M0, T2N0M0) NSCLC in adult patients (age 18 years or older) whose tumor is deemed operable but decline surgery?

Question 3

- a. What are the comparative short- and long-term benefits and harms of local therapies given with palliative or curative intent to patients with stage IIIa NSCLC with endoluminal obstruction of the trachea, main stem, or lobar bronchi and recurrent or persistent thoracic symptoms such as hemoptysis, cough, dyspnea, and postobstructive pneumonitis?
- b. What are the comparative short- and long-term benefits and harms of local palliative therapies in patients with advanced stage (IIIb or IV) NSCLC with endoluminal obstruction of the trachea, main stem, or lobar bronchi and recurrent or persistent thoracic symptoms such as hemoptysis, cough, dyspnea, and postobstructive pneumonitis?

PICOTS Framework

- **Population(s)**

KQs 1 and 2

Adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 and T2N0M0) NSCLC who:

- Are not deemed surgical candidates because of the documented presence of contraindications to major surgery, for example, cardiac insufficiency, poor pulmonary function, presence of severe intercurrent illness, or poor performance status (KQ 1)
- May otherwise be deemed surgical candidates according to current clinical criteria but decline surgery (KQ 2)

KQ 3

Adult patients (age 18 years or older) with advanced stage (IIIa, IIIb, or IV) NSCLC who have endoluminal obstruction of the trachea, main stem, or lobar bronchi and recurrent or persistent thoracic symptoms such as hemoptysis, cough, dyspnea, and postobstructive pneumonitis and are treated with:

- KQ 3a: Curative or palliative intent (stage IIIa)
- KQ 3b: palliative intent (stage IIIb/IV)

- **Interventions**

- No definitive surgical intervention will be considered for any KQ.



- For KQs 1 and 2, only single interventions will be compared, for example two different conformal RT methods or RFA compared to a conformal RT method.
- For KQ 3, combinations may be considered, for example endobronchial debridement plus a stent, compared to debridement alone; or, combination of 2D-RT with BT compared to RT alone.
- Because systemic therapy (chemotherapy) may be used with radiotherapy or local interventional methods in stage III or greater patients, we will collect that information to use in categorizing and assessing outcomes to ensure relevant and appropriate comparisons are made, particularly as they relate to possible harms. Such comparisons may be segregated and reported accordingly if it is not possible to discern interventional therapeutic effects.

KQs 1 and 2

- Conformal RT methods (including stereotactic body radiotherapy, 3D-CRT, and IMRT)
- PBRT
- Radiofrequency ablation

KQ 3

- Conventional 2D external beam radiotherapy
- Conformal radiotherapy methods (including stereotactic body radiotherapy, 3D-CRT, and IMRT)
- BT
- RFA
- Cryoablation
- Laser therapy
- Endobronchial debridement and stents

● **Comparators**

KQs 1 and 2

- Interventions will be compared to each other as appropriate and noted above.

KQ 3

- Interventions will be compared to each other as appropriate and noted above.

● **Outcomes**

KQ 1 and 2



- Final health outcomes: Overall survival, cancer-specific survival, performance status, and pulmonary quality of life
- Intermediate outcomes: Local control
- Adverse outcomes: Includes, but not limited to, RT-associated adverse events (e.g., pneumonitis, cardiotoxicity, hemoptysis, dermatitis, etc.), non-RT-associated adverse events (e.g., pneumothorax, hemothorax, pleural effusion)

KQ 3

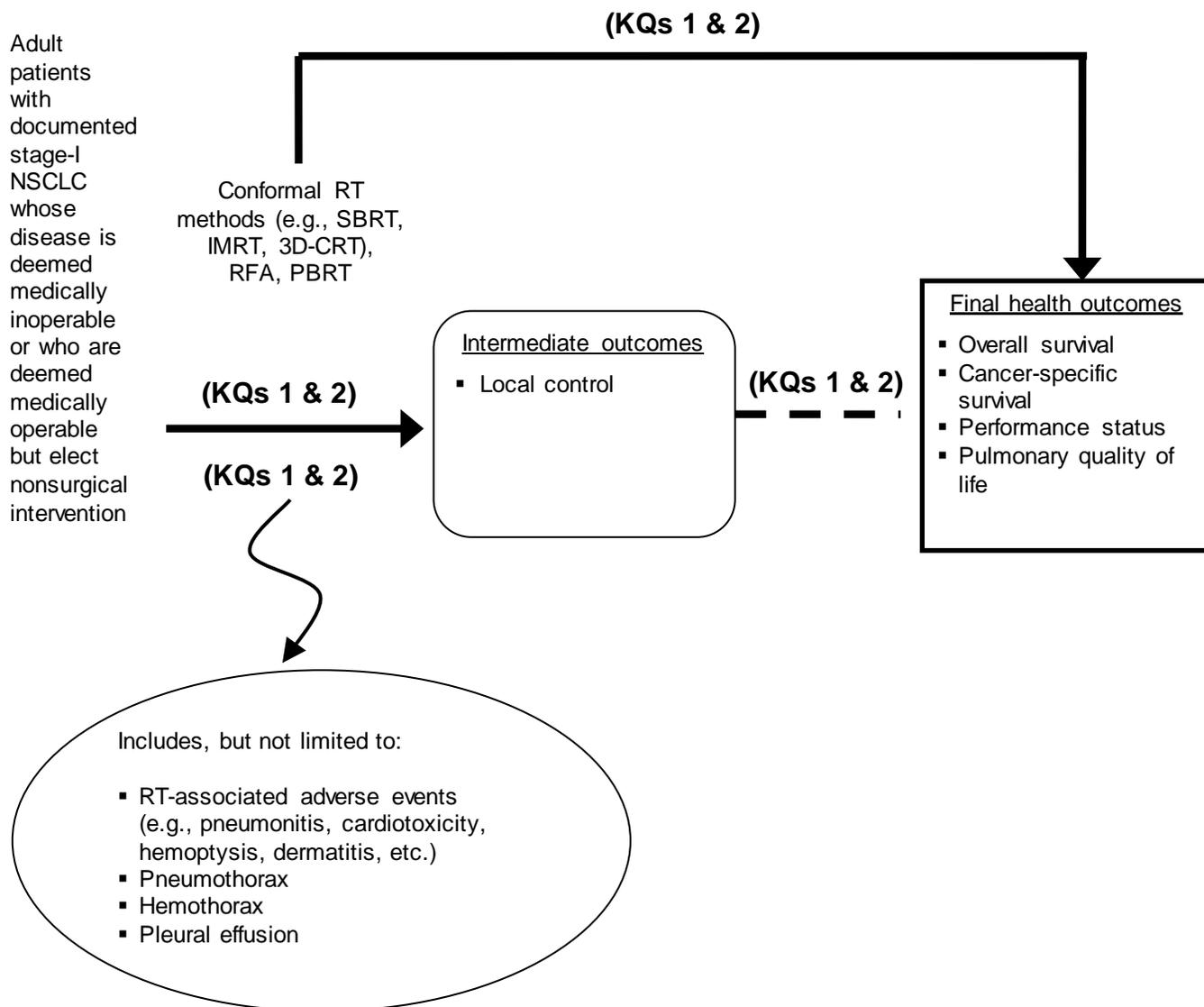
- Final health outcomes: Overall survival, performance status, pulmonary quality of life
 - Intermediate outcomes: Local control, lung function (e.g., forced expiratory volume 1), pulmonary symptoms (e.g., dyspnea, hemoptysis), respiratory tract infection
 - Adverse outcomes: Includes, but not limited to, RT-associated adverse events (e.g., pneumonitis, cardiotoxicity, hemoptysis, dermatitis, etc.), non-RT-associated adverse events (e.g., pneumothorax, pleural effusion, transesophageal fistula, pericardial effusion)
-
- **Timing**
 - The relevant periods occur at the time of treatment through followup over months (palliation) or years (overall survival).
 - **Settings**
 - Inpatient and outpatient

III. Analytical Frameworks

Figure 1 shows the analytical framework for KQs 1 and 2. This figure depicts the potential impact of using lung-directed nonsurgical definitive therapies for adult patients (age 18 years or older) with documented (clinical or biopsy) stage-I NSCLC, defined as either T1N0M0 or T2N0M0, on both intermediate outcomes and final health outcomes. Direct evidence of the impact of the various therapies on health outcomes, including adverse effects, is shown by solid lines. Intermediate outcomes, such as local control and recurrence, may have an association with final health outcomes (dotted line).

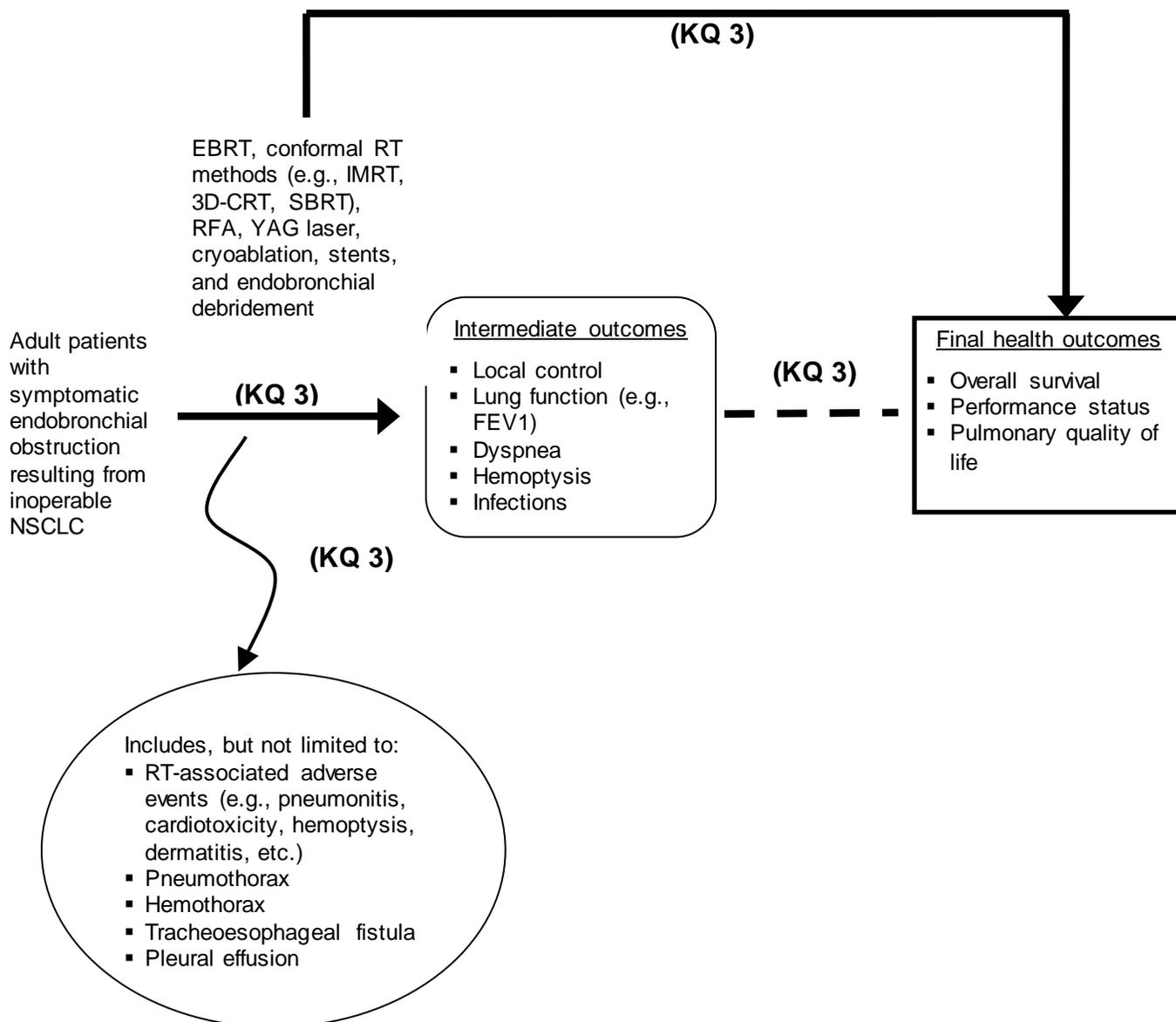
Figure 2 depicts the analytical framework for KQ 3. It depicts the potential impact of using lung-directed therapies, either palliative for stages IIIa, IIIb, or IV NSCLC or curative for adult patients (age 18 years or older) with stage IIIa disease, on both intermediate outcomes and final health outcomes. Direct evidence of the impact of the various therapies on health outcomes, including adverse effects, is shown by solid lines. Intermediate outcomes, such as local control, recurrence, lung function (e.g., FEV1), pulmonary symptoms (e.g., dyspnea, bleeding), and respiratory tract infection may have an association with final health outcomes (dotted line).

Figure 1. Analytical framework for comparative effectiveness of local nonsurgical definitive therapies for adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 or T2N0M0) non-small cell lung cancer whose disease is deemed medically inoperable or whose disease is deemed operable but elect nonsurgical intervention



Abbreviations: IMRT = intensity-modulated radiation therapy; KQ = key question; NSCLC = non-small cell lung cancer; PBRT = proton beam radiotherapy; RFA = radiofrequency ablation; RT = radiotherapy; SBRT = stereotactic body radiation therapy; 3D-CRT = three-dimensional conformal radiotherapy

Figure 2. Analytical framework for comparative effectiveness of local curative (stage IIIa) or palliative (stage IIIa, IIIb, or IV) therapies for adult patients (age 18 years or older) with symptomatic inoperable endobronchial obstruction due to non-small cell lung cancer



Abbreviations: EBRT = external beam radiation therapy; FEV = forced expiratory volume; IMRT = intensity-modulated radiation therapy; KQ = key question; NSCLC = non-small cell lung cancer; RFA = radiofrequency ablation; RT = radiotherapy; SBRT = stereotactic body radiation therapy; 3D-CRT = three-dimensional conformal radiotherapy; YAG = yttrium-aluminum-garnet

IV. Methods

Methodological practices to be followed in this review will be derived from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*²⁷ (hereafter *Methods Guide*) and its subsequent updates.

A. Study Selection Criteria

We will seek to include only comparative studies, preferably randomized controlled trials (RCTs), but also nonrandomized comparative studies (including case-control and cohort studies) that report on the populations, comparisons, interventions, and outcomes that are part of the PICOTS. We will include noncomparative observational studies (case series) to assess comparative effectiveness in the absence of direct comparative studies. Case series will only be included when they discuss previously unreported outcomes. To classify observational study designs, we will use the system developed by Briss and colleagues.²⁸

Editorials, commentaries, case reports, and animal studies will be excluded. The bibliographies of review articles and systematic reviews published within the past 5 years will be examined for primary studies that may have eluded our electronic searches. Primary studies published prior to January 1, 1995, will be excluded to assure we are considering current techniques and methods.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

The databases listed below will be searched electronically by a medical librarian for citations from January 1995 through December 2011:

- MEDLINE[®]
- EMBASE[®]
- Cochrane Controlled Trials Register

The search will be limited to English-language studies based on the following rationale. First, there is evidence to suggest that language restrictions do not change results of systematic review for conventional medical interventions.²⁹ Second, input from the TEP suggested that most if not all of the pivotal studies in this area would be captured in the English-language evidence base and that restriction to English would not introduce bias.

Our search strategy will use the National Library of Medicine's Medical Subject Headings (MeSH[®]) keyword nomenclature developed for MEDLINE[®] and adapted for use in other databases. The searches will be limited to studies of human subjects, published in English, as shown in Appendix 1.

Grey literature will be sought by searching for clinical trials (Clinicaltrials.gov), the U.S. Food and Drug Administration (FDA) Web site, and relevant conference abstracts for data pertaining to the interventions under consideration used to definitively treat stage-I NSCLC or

treat symptomatic endobronchial obstruction secondary to advanced (stage IIIa, IIIb, or IV) NSCLC. We will review Scientific Information Packets from the Scientific Resource Center. Study authors will be contacted for unpublished results if the primary authors concur that, if obtained, evidence could impact results meaningfully (i.e., alter GRADE analyses).

C. Data Management

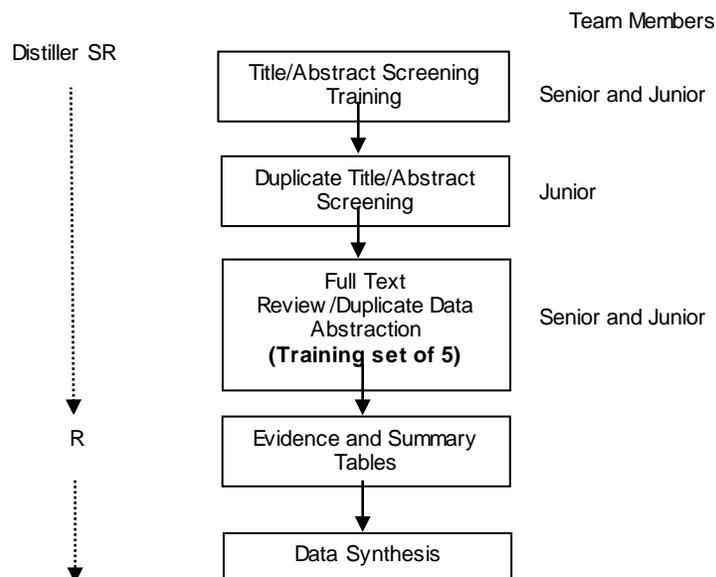
Electronic search results will be transferred into an EndNote[®] bibliographic database and subsequently into Distiller SR for study screening and selection. Using the study-selection criteria (outlined under Study Selection Criteria above in this section) for screening titles and abstracts, each citation will be marked as: 1) eligible for review as full-text articles; 2) ineligible for full-text review. Reasons for exclusion will not be noted at this point. At least one training set of 50 to 100 titles and abstracts for each KQ will be examined initially by all team members to assure uniform application of screening criteria. Subsequent sets will be assessed until concordance is established among the team. Ultimate title and abstract screening will be performed in duplicate by two junior-level Evidence-based Practice Center (EPC) team members. To be excluded, a study must be independently excluded by both team members. In the cases where they disagree, Distiller SR will, by default, include and forward the reference for adjudication by the team leader.

A test set of a minimum 5 to 10 papers relevant to the three KQs will be evaluated in full text by junior and senior team members, including the team leader, to ensure selection criteria are applied correctly. Additional evaluations will be performed as needed to assure concordance among the selectors. Subsequently, two junior team members will review full-text articles in duplicate to determine their inclusion in the systematic review. Weekly team meetings will be held to discuss progress and to ensure the team leader is aware of difficulties or problems in this process. Both screeners must agree on exclusions; disagreements will resolved by the senior team leader. A record of the reason for exclusion of each paper retrieved will be kept in the Distiller SR database. While a paper may be excluded for multiple reasons, only one will be recorded.

Data elements will be abstracted directly into tables created in Distiller SR, as defined below. A minimum training set of five primary articles will be abstracted by all team members. Ultimate data abstraction will be performed in duplicate by junior team members, with discrepancies resolved by the senior team leader.

Abstracted data will be transferred from Distiller SR to R.³⁰ The latter will be used to compile study-level and summary tables in Microsoft[®] Excel format for inclusion in the report. The entire process is shown schematically in Figure 3.

Figure 3. Schematic for data management



Data Elements

The following data elements from the intervention studies will be abstracted or recorded as not reported. The data elements to be abstracted will include the following:

- Quality Assessment
 - Number of participants and flow of participants through steps of study
 - Treatment-allocation methods (including concealment for RCTs)
 - Use of blinding (RCTs only)
 - Study design (prospective versus retrospective)
 - Use of an independent outcome assessor

Additional elements are described below under Assessment of Methodological Quality of Individual Studies.

- Patient characteristics, including:
 - Age (excluding pediatric patients, 18 years or younger)
 - Sex
 - Race/ethnicity
 - Rationale for determination of medical inoperability
 - Medical comorbidities
 - Tumor location
 - Tumor staging method



- Biopsy-proven
 - Positron emission tomography (PET) or PET/CT
 - Clinically staged
 - Unclear (method not reported)
 - Tumor histology
 - Treatment setting
 - Outpatient
 - Inpatient
- Treatment characteristics, including:
 - Type of lung-directed therapy(ies)
 - RT characteristics (e.g., total dose, fractionation, etc.)
 - Other prior or concurrent treatment modalities (e.g., systemic chemotherapy)
 - Number of prior lines of treatment
 - Methods used to determine tumor recurrence (e.g., PET, PET/CT, CT)
- Outcome Assessment
 - Identified primary outcome (see Analytical Frameworks and PICOTS above)
 - Identified secondary outcomes (see Analytical Frameworks and PICOTS above)
 - Response criteria
 - Followup frequency and duration
 - Cause of death (e.g., comorbidity or cancer-specific)
- Details of data analysis, including:
 - Statistical analyses (statistical test/estimation results)
 - Summary measures
 - Sample variability measures
 - Precision of estimate
 - *p* values
- Regression modeling techniques
 - Model type
 - Candidate predictors and methods for identifying candidates
 - Univariate analysis results
 - Selected predictors and methods for selecting predictors
 - Testing of assumptions
 - Inclusion of interaction terms
 - Multivariable model results
 - Discrimination or validation methods and results
 - Calibration or “goodness-of-fit” results

The same abstraction tables will be used for comparative and single-arm studies, although some elements may not apply to the latter (e.g., description of the control group). We will report outcome data in strata according to prognostic or other patient-related factors such as tumor stage, providing they are reported separately or can be inferred from the study in question.

D. Assessment of Methodological Quality of Individual Studies

Definition of Ratings Based on Criteria

In adherence with the *Methods Guide*,²⁷ the general approach to grading individual comparative studies will be performed by using a method used by the U.S. Preventive Services Task Force.³¹ The quality of the abstracted studies will be assessed by two independent reviewers. Discordant quality assessments will be resolved with input from a third reviewer, if necessary.

- The quality of studies will be assessed on the basis of the following criteria:
 - Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., other concomitant care) were distributed equally among groups
 - Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
 - Important differential loss to followup or overall high loss to followup
 - Measurements: equal, reliable, and valid (includes masking of outcome assessment)
 - Clear definition of interventions
 - All important outcomes considered
 - Analysis: adjustment for potential confounders and intention-to-treat analysis
- Intervention studies will be rated according to one of three quality categories:

Good. Meets all criteria; comparable groups are assembled initially and maintained throughout the study (followup at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair. Studies are graded “fair” if any or all of the following problems occur, without the fatal flaws noted in the “poor” category below: In general, comparable groups are assembled initially, but some questions remain about whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and are generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis has been done for RCTs.



Poor. Studies are graded “poor” if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups; and key confounders are given little or no attention; lack of masked outcome assessment; and for RCTs, intention-to-treat analysis is lacking.

- The quality of included nonrandomized comparative intervention studies will also be assessed based on a selection of items proposed by Deeks and colleagues³² to inform the approach used by the U.S. Preventive Services Task Force³¹ as follows:
 - Was sample definition and selection prospective or retrospective?
 - Were inclusion/exclusion criteria clearly described?
 - Were participants selected to be representative?
 - Was there an attempt to balance groups by design?
 - Were baseline prognostic characteristics clearly described and groups shown to be comparable?
 - Were interventions clearly specified?
 - Were participants in treatment groups recruited within the same time period?
 - Was there an attempt by investigators to allocate participants to treatment groups in an attempt to minimize bias?
 - Were concurrent/concomitant treatments clearly specified and given equally to treatment groups?
 - Were outcome measures clearly valid, reliable, and equally applied to treatment groups?
 - Were outcome assessors blinded?
 - Was the length of followup adequate?
 - Was attrition below an overall high level (<20%)?
 - Was the difference in attrition between treatment groups below a high level (<15%)?
 - Did the analysis of outcome data incorporate a method for handling confounders such as statistical adjustment?

- The quality of included single-arm intervention studies will be assessed based on a set of study characteristics proposed by Carey and Boden,³³ as follows:
 - Clearly defined question
 - Well-described study population
 - Well-described intervention
 - Use of validated outcome measures
 - Appropriate statistical analyses
 - Well-described results
 - Discussion and conclusion supported by data
 - Funding source acknowledged

E. Data Synthesis

Whether or not this evidence review will incorporate formal data synthesis (e.g., meta-analysis) will be determined after completing the formal literature search, screen, and study inclusion. Procedures used for meta-analysis will conform to methods outlined by the AHRQ EPC program in the *Methods Guide* and elsewhere.^{27, 34, 35}

When appropriate (e.g., similar instruments used or standardized effect measures relevant and interpretable), outcome measures will be pooled according to AHRQ guidance, and synthesized in R³⁶ using the meta³⁷ and metafor³⁸ packages. Clinical heterogeneity and appropriateness for pooling will be judged on the basis of study characteristics in concert with subject matter knowledge. Because the goal of any pooling is to estimate unconditional effects,³⁹ random-effects models will be used. The magnitude of statistical heterogeneity will be examined using I² acknowledging potential limitations⁴⁰ and, when present (e.g., exceeding 25%), explored in meta-regressions.⁴¹ Evidence for possible publication bias will be explored using funnel plots.

Potential subgroups effects for benefits will be examined as reported but may include: patient age, comorbidities, tumor size, tumor location, intervention type, and previous therapy. Outcomes will be summarized and reported corresponding to the order specified and by intervention in the KQs.

Grading the Evidence for Each Key Question

Studies will be assessed for relevance against target populations, interventions of interest, and outcomes of interest. The system used for rating the strength of the overall body of evidence is outlined in the *Methods Guide*²⁷ and is based on a system developed by the GRADE Working Group.⁴² This system explicitly addresses the following domains: risk of bias, consistency, directness, and precision. The grade of evidence strength is classified into the following four categories:

- **High.** High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate.** Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low.** Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- **Insufficient.** Evidence is either unavailable or does not permit estimation of an effect.

Additional (optional) domains including strength of association, publication bias, coherence, dose-response relationship, and residual confounding will be addressed if appropriate.

Specific outcomes and comparisons to be rated will depend on the evidence found in the literature review. The grade rating will be made by independent reviewers, and disagreements will be resolved by consensus adjudication.

F. Assessing Applicability

Applicability of findings in this review will be assessed according to the AHRQ *Methods Guide* using the PICOS (Population, Intervention, Comparator, Outcome, and Setting) framework.^{27, 43} Included studies will be assessed for relevance against target populations, interventions and comparators of interest, and outcomes of interest.

It is anticipated that results will be applicable only to the specialized populations of interest by KQ. Factors to consider for this include the following:

- Patient characteristics, including:
 - Age (excluding pediatric patients, 18 years or younger)
 - Sex
 - Race/ethnicity
 - Rationale for determination of medical inoperability
 - Medical comorbidities
- Tumor location
- Tumor staging method
 - Biopsy-proven
 - PET or PET/CT
 - Clinically staged
 - Unclear (method not reported)
- Tumor histology
- Treatment setting
 - Outpatient
 - Inpatient

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VI. Definition of Terms

None

VII. Summary of Protocol Amendments

None

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to

provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC team disclosures:

The EPC Team has no conflicts of interest to disclose.

XIII. Role of the Funder:

This project was funded under Contract No. xxx-xxx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

APPENDIX 1.

The search strategies for the CER are as follow:

PubMed (MEDLINE) – December 12, 2011

Stage I

"Carcinoma, Non-Small-Cell Lung"[Mesh] OR ("Lung Neoplasms"[Mesh] OR "lung cancer")
AND ("non-small-cell" OR "non-small cell" OR "non small cell")

AND

"stage I" OR "stage one" OR "stage 1" OR T1N0M0 OR T2N0M0 OR early OR inoperable OR
unoperable OR nonoperable OR decline* OR refuse*

AND

"Brachytherapy"[Mesh] OR "Protons"[Mesh] OR "Radiotherapy, Intensity-Modulated"[Mesh]
OR "Radiotherapy, Conformal"[Mesh] OR "Ablation Techniques"[Mesh] OR
"Radiotherapy"[Mesh] OR "radiotherapy "[Subheading] OR "radiofrequency ablation" OR
(radiofrequency AND ablation) OR RFA OR radiotherapy OR radiation OR "external beam" OR
"3D conformal" OR "3-D Conformal" OR "intensity modulated radiotherapy" OR IMRT OR
brachytherapy OR "stereotactic radiotherapy" OR "stereotactic body radiotherapy" OR ("proton
beam" AND (radiation OR therapy OR radiotherapy))

AND

English language/Humans as limits

Advanced

"Carcinoma, Non-Small-Cell Lung"[Mesh] OR ("Lung Neoplasms"[Mesh] OR "lung cancer")
AND ("non-small-cell" OR "non-small cell" OR "non small cell")

AND

"stage III" OR "stage 3" OR "stage three" OR "stage IIIa" OR "stage IIIb" OR "stage IV" OR
"stage 4" OR "stage four" OR advanced

AND

"Brachytherapy"[Mesh] OR "Protons"[Mesh] OR "Radiotherapy, Intensity-Modulated"[Mesh]
OR "Radiotherapy, Conformal"[Mesh] OR "Ablation Techniques"[Mesh] OR
"Radiotherapy"[Mesh] OR "radiotherapy "[Subheading] OR "radiofrequency ablation" OR
(radiofrequency AND ablation) OR RFA OR radiotherapy OR radiation OR "external beam" OR
"intensity modulated radiotherapy" OR IMRT OR brachytherapy OR "stereotactic radiotherapy"
OR "stereotactic body radiotherapy" OR ("proton beam" AND (radiation OR therapy OR
radiotherapy)) OR "Stents"[Mesh] OR stent* OR ("Debridement"[Mesh] OR debridement)
AND (endoscopy OR endoscopic OR endobronchial))

AND

English language/Humans as limits

EMBASE 12/13/11

Stage I

'non-small-cell lung cancer'/exp OR ('lung neoplasms'/exp OR 'lung cancer'/exp AND ('non-
small-cell' OR 'non-small cell' OR 'non small cell' OR nslc))

AND

"stage I" OR "stage one" OR "stage 1" OR T1N0M0 OR T2N0M0 OR early OR inoperable OR unoperable OR nonoperable OR decline* OR refuse*

AND

"radiofrequency ablation" OR (radiofrequency AND ablation) OR RFA OR radiotherapy OR radiation OR "external beam" OR "3D conformal" OR "3-D Conformal" OR "intensity modulated radiotherapy" OR IMRT OR brachytherapy OR "stereotactic radiotherapy" OR "stereotactic body radiotherapy" OR ("proton beam" AND (radiation OR therapy OR radiotherapy))

AND

English language/Humans as limits

AND NOT MEDLINE

Advanced

'non-small-cell lung cancer'/exp OR ('lung neoplasms'/exp OR 'lung cancer'/exp AND ('non-small-cell' OR 'non-small cell' OR 'non small cell' OR nscl))

AND

'stage iii' OR 'stage 3' OR 'stage three' OR 'stage iiiia' OR 'stage iiib' OR 'stage iv' OR 'stage 4' OR 'stage four' OR advanced

AND

'radiofrequency ablation'/exp OR ('radiofrequency'/exp AND ablation) OR rfa OR 'radiotherapy'/exp OR 'radiation'/exp OR 'external beam' OR 'intensity modulated radiotherapy'/exp OR 'imrt'/exp OR 'brachytherapy'/exp OR 'stereotactic radiotherapy' OR 'stereotactic body radiotherapy'/exp OR ('proton beam'/exp AND ('radiation'/exp OR 'therapy'/exp OR 'radiotherapy'/exp)) OR stent* OR ('debridement'/exp AND ('endoscopy'/exp OR endoscopic OR endobronchial))

AND

English language/Humans as limits

AND NOT MEDLINE

COCHRANE

1. MeSH descriptor Carcinoma, Non-Small-Cell Lung explode all trees
2. (brachytherapy):ti,ab,kw or (radiotherapy):ti,ab,kw or (ablation):ti,ab,kw or (radiation):ti,ab,kw or (stereotactic):ti,ab,kw
3. (#1 AND #2)
4. (stent*):ti,ab,kw or (proton):ti,ab,kw or (radiofrequency):ti,ab,kw or (debridement):ti,ab,kw
5. ((#1 AND #4)
6. (#3 OR #5)