



Effective Health Care Program

Local Nonsurgical Therapies for Stage I and Symptomatic Obstructive Non-Small-Cell Lung Cancer

Executive Summary

Background

Non-small-cell lung cancer (NSCLC) refers to any type of epithelial lung cancer other than small-cell lung cancer.¹ The disease arises from epithelial cells of the lung, from the central bronchi to terminal alveoli. The histological type correlates with site of origin, reflecting the variation in respiratory tract epithelium by location. The most common types of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Several other types occur less frequently; all can occur in unusual histological variants. Squamous cell carcinoma typically originates near a central bronchus. Adenocarcinoma and adenocarcinoma in situ (formerly called bronchioalveolar carcinoma) usually arise in peripheral lung tissue. Adenocarcinomas are frequently associated with cigarette smoke but may also occur in patients who have never smoked.

More than 1 million deaths are attributed per year to NSCLC, making it the leading cause of cancer-related mortality worldwide.² In the United States, lung cancer is the leading cause of cancer death, and an estimated 222,520 cases were expected to be diagnosed in 2010, with 157,300 deaths due to the disease.²

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

NSCLC may be symptomatic at presentation or it may be incidentally discovered at a routine chest imaging examination. The most common symptoms at presentation are progressive cough



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or chest pain. Other presenting symptoms include hemoptysis, malaise, weight loss, dyspnea, and hoarseness. Symptoms may result from local invasion or compression of adjacent thoracic structures, such as compression of the esophagus causing dysphagia, compression of the laryngeal nerves causing hoarseness, or compression involving the superior vena cava causing facial edema and distension of the superficial veins of the head and neck. Symptoms from distant metastases may also be present and include neurological defect or personality change from brain metastases or pain from bone metastases. Physical examination may identify enlarged supraclavicular lymphadenopathy, pleural effusion or lobar collapse, unresolved pneumonia, or signs of associated disease, such as chronic obstructive pulmonary disease or pulmonary fibrosis.

The prognosis of an NSCLC patient and the subsequent treatment plan are a function of disease stage.³ NSCLC stage is defined by the TNM system, which was initially developed by the Union Internationale Contre le Cancer (UICC) and the American Joint Committee for Cancer Staging (AJCC). The TNM system takes into account the size of the primary tumor (T), the extent of regional lymph node involvement (N), and the presence or absence of distant metastases (M).⁴ The UICC and AJCC have adopted the current Revised International System for Staging Lung Cancer, which is based on information from a clinical database of nearly 70,000 patients.⁴ Imaging methods used to stage NSCLC patients may include 18F-fluorodeoxyglucose positron emission tomography (FDG PET), computed tomography (CT), or magnetic resonance imaging (MRI).⁵ The presence of symptoms, physical signs, or laboratory findings, or perceived risk of distant metastasis ultimately drive evaluation for nodal and distant metastatic disease. Bone scans, FDG PET, CT, or MRI may be performed if initial assessments suggest nodal or more distant metastases, or if a patient with more advanced disease is under consideration for aggressive local and combined-modality treatments. Surgical staging of the mediastinum is considered the standard to evaluate local nodal status.

Treatment Options for NSCLC

NSCLC patients can be divided into three general groups that reflect the extent of disease, which in turn dictates the initial treatment approach, not considering systemic therapies:

- Surgically resectable disease (generally stage I, stage II, and selected stage III tumors)

- Potentially operable or inoperable locally (T3–T4) or regionally (N2–N3) advanced disease, including endoluminal lesions
- Inoperable distant metastatic disease, including distant metastases (M1) that are found at the time of diagnosis

Surgery is the standard of care for patients with resectable stage I NSCLC. However, alternative treatments are needed for two subsets of stage I NSCLC patients. First is a subset that comprises about 20–30 percent of stage I patients: those who have resectable tumors but are deemed medically inoperable, primarily because of preexisting diminished cardiac reserve, poor pulmonary function, and poor performance status.^{6–9} A second, much less common subset comprises patients who are deemed operable but decline surgery. It is assumed that medically inoperable patients are more likely to die from intercurrent illness than from lung cancer; however, evidence exists to question this assumption.⁹ For example, among a group of 128 patients with stage I or II NSCLC treated between 1994 and 1999, 49 did not receive any surgical treatment, as they were deemed medically inoperable, and yet 53 percent of them died due to lung cancer.¹⁰ Among 1,432 untreated medically inoperable stage I NSCLC patients reported to a registry in California, the lung cancer–specific survival rate at 5 years was 16 percent, suggesting the need for alternative interventions in such patients.¹¹

This report aims to compare the effectiveness and harms of local nonsurgical therapies for medically inoperable NSCLC stage I patients, medically operable NSCLC stage I patients who refuse surgery, or patients with inoperable NSCLC who have symptoms secondary to the presence of an endoluminal lesion. Comparisons of ablation versus surgery or systemic chemotherapy versus local nonsurgical therapy are outside the scope of this report.

Local Nonsurgical Treatment Options for Stage I NSCLC

Radiotherapy has a role in the definitive treatment of patients with stage I NSCLC who are deemed medically inoperable or those who decline surgery.^{7,9} Ideally, radiotherapy balances delivery of a cytotoxic dose of ionizing radiation to the tumor volume, attempting to minimize adverse effects of radiation on adjacent normal lung tissue and thoracic structures. Several radiotherapy modalities have been used to treat patients with stage I NSCLC. Conventional wide-field two-dimensional radiation therapy (2DRT) has been used extensively to treat medically inoperable patients with stage I NSCLC.

Delivery of radiation to a total dose that ranged from 31 to 103 Gray (Gy), in daily fractions of 1.8-2 Gy, has been reported to produce overall survival rates of 17 percent to 42 percent among patients with early-stage disease.⁸ However, conventional 2DRT is no longer in routine use in modern radiation oncology practice in this setting and thus was not considered in this comparative effectiveness review (CER).

A quest to improve on survival rates achieved with 2DRT has led to development of conformal radiotherapy methods for definitive (curative) treatment of inoperable patients with stage I NSCLC. Conformal radiotherapy refers to modalities in which cytotoxic radiation beams are “shaped” to cover the tumor volume plus a surrounding tissue margin to treat microscopic disease that may reside there. Photon-based modalities include three-dimensional conformal radiation therapy (3DRT); intensity-modulated radiation therapy (IMRT); and stereotactic body radiation therapy (SBRT), which is also known as stereotactic ablative radiotherapy.¹²⁻¹⁴ For purposes of this report, we use the term “SBRT.” Charged particle–based therapy such as proton beam radiotherapy (PBRT) is also available.¹⁵

The optimal definitive external radiotherapy modality is not defined for patients with medical contraindications (medically inoperable patients) or for those with stage I NSCLC who elect nonsurgical treatment.¹⁴ All radiotherapy procedures listed above are time intensive, require significant training, and necessitate substantial advance planning.^{13,16} Institutional quality control processes are required to assure their safe and effective use, in particular IMRT.¹⁷ Analysis of the application of PBRT to NSCLC presents challenges because of the small number of institutions that have experience with this technique and small reported patient numbers.¹⁵

Interventional treatment options for stage I NSCLC include radiofrequency ablation (RFA).^{18,19} Percutaneous RFA is a minimally invasive technique that uses high-frequency electric currents to heat and destroy tumors and is typically performed in a single session.²⁰ The most frequent complication of RFA is pneumothorax.²¹ Analysis of the application of RFA to NSCLC presents challenges because of the small number of institutions that have experience with this technique and small number of patients.^{15,20,22}

Local Nonsurgical Treatment Options for Symptomatic Endobronchial NSCLC

Patients with airway obstruction from nonresectable primary or recurrent endoluminal lung tumors comprise 20–30 percent of NSCLC cases and manifest symptoms

of disabling dyspnea, cough, and hemoptysis.^{23,24} Up to 40 percent of lung cancer deaths may be attributed to such locoregional disease. Management of these patients is a significant challenge. For example, the ability to promptly alleviate airway distress may be lifesaving, as some patients may succumb to suffocation within hours of presentation.²⁴⁻²⁶ Patients with such advanced disease often require emergency treatment to relieve airway obstruction or stop bleeding. These interventions are palliative but are performed in some patients with curative intent.

Patients with good performance status may benefit from external-beam radiotherapy (EBRT), which comprises conventional 2DRT or conformal methods, outlined above, to ameliorate symptoms (hemoptysis, cough, chest pain, dyspnea, obstructive pneumonia, dysphagia, etc.) associated with an airway obstructive tumor.²⁶ However, if they have already been heavily pretreated or the tumor is located too close to radiosensitive organs or other anatomic structures, interventional options may become necessary.

Brachytherapy is another option for relieving airway obstruction and can be used alone or with EBRT to boost the total dose of irradiation used.^{26,27} Brachytherapy has been used in combination with high-dose EBRT as a potentially curative primary treatment in selected cases. Serious complications have been described with brachytherapy, including massive hemoptysis, tracheoesophageal fistulas, bronchial stenosis, and radiation bronchitis.²⁷

The role of brachytherapy for the palliative treatment of symptomatic patients with airway obstruction is unclear. Brachytherapy has been used as a palliative treatment in case of endobronchial tumor recurrence after EBRT. Brachytherapy also may be an option for patients in whom EBRT fails to relieve symptoms or those with an obstructive endobronchial lesion who require lung reexpansion before or in conjunction with EBRT.²⁶

Several interventional methods involve tumor debulking to palliate symptoms in patients with advanced endobronchial NSCLC.^{19,25,26,28} Interventional bronchoscopy with mechanical tumor debulking and stent placement can rapidly reestablish airway patency and relieve dyspnea and respiratory distress in patients with airway obstruction due to a malignant endoluminal tumor.^{25,28} Debulking and stent placement may be complemented by subsequent application of radiotherapy to extend the durability of palliation and may offer definitive therapy for local tumors.

Laser resection involving the neodymium-doped yttrium aluminum garnet (Nd-YAG) laser and photodynamic

therapy (PDT) using porfimer sodium have been investigated in this setting, with suggestion of symptomatic improvement in some cases.¹⁹ RFA also has been used in cryosurgery.

Objectives

This CER is intended to be a comprehensive systematic review of the relative benefits and harms of lung-directed nonsurgical therapies in two disease settings encompassing three distinct patient populations. The disease setting and patient populations are defined in the Key Questions section. Available therapies include conformal radiation modalities (3DRT, IMRT, SBRT, PBRT) and interventional methods such as RFA. Likewise, numerous methods are used to treat patients with symptomatic malignant airway obstruction: EBRT methods, brachytherapy, surgical debridement and stent placement, and others (e.g., Nd-YAG laser, cryoablation).

Surgery is the standard of care for eligible patients with stage I NSCLC. However, a substantial subset of stage I NSCLC patients exists for whom surgery is contraindicated due to the existence of underlying comorbidities. Alternatives also are needed for another smaller proportion of stage I patients who are medically operable but decline surgery. Comparison of outcomes with alternative procedures to those achieved with surgery is outside the scope of this CER. Instead, the CER is focused on comparison of local nonsurgical modalities for inoperable patients in Key Question 1 and for operable patients in Key Question 2.

Key Question 3 addresses the comparative benefits and harms of local nonsurgical therapies in patients with inoperable NSCLC who have symptoms secondary to the presence of an endoluminal lesion. The optimal approach in these patients is not established. These patients often require urgent care; typically, they have a short expected lifespan and interventions are often palliative.

All of the alternative modalities under consideration are clinically relevant and merit comparative evaluation due to uncertainty surrounding their optimal use in these settings. Alternatives to surgery are important to health care providers, patients, and policymakers, given the substantial disease burden of NSCLC, especially in the elderly population.

Key Questions and Analytical Framework

The Key Questions and CER analytical frameworks (Figures A and B) are structured to be consistent with the populations, interventions, comparisons, outcomes, timing, and settings (PICOTS) framework (Table A), as laid out in

the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” (Methods Guide).²⁹

The Key Questions are:

Key Question 1. What are the comparative benefits and harms of local nonsurgical definitive 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?

Key Question 2. What are the comparative benefits and harms of local nonsurgical definitive therapies for documented (clinical or biopsy) stage I (T1N0M0, T2N0M0) NSCLC in adult patients (age 18 years or older) who are deemed operable but decline surgery?

Key Question 3. What are the comparative short- and long-term benefits and harms of local nonsurgical therapies given with palliative or curative intent to patients with endoluminal NSCLC causing obstruction of the trachea, main stem, or lobar bronchi and recurrent or persistent thoracic symptoms such as hemoptysis, cough, dyspnea, and postobstructive pneumonitis?

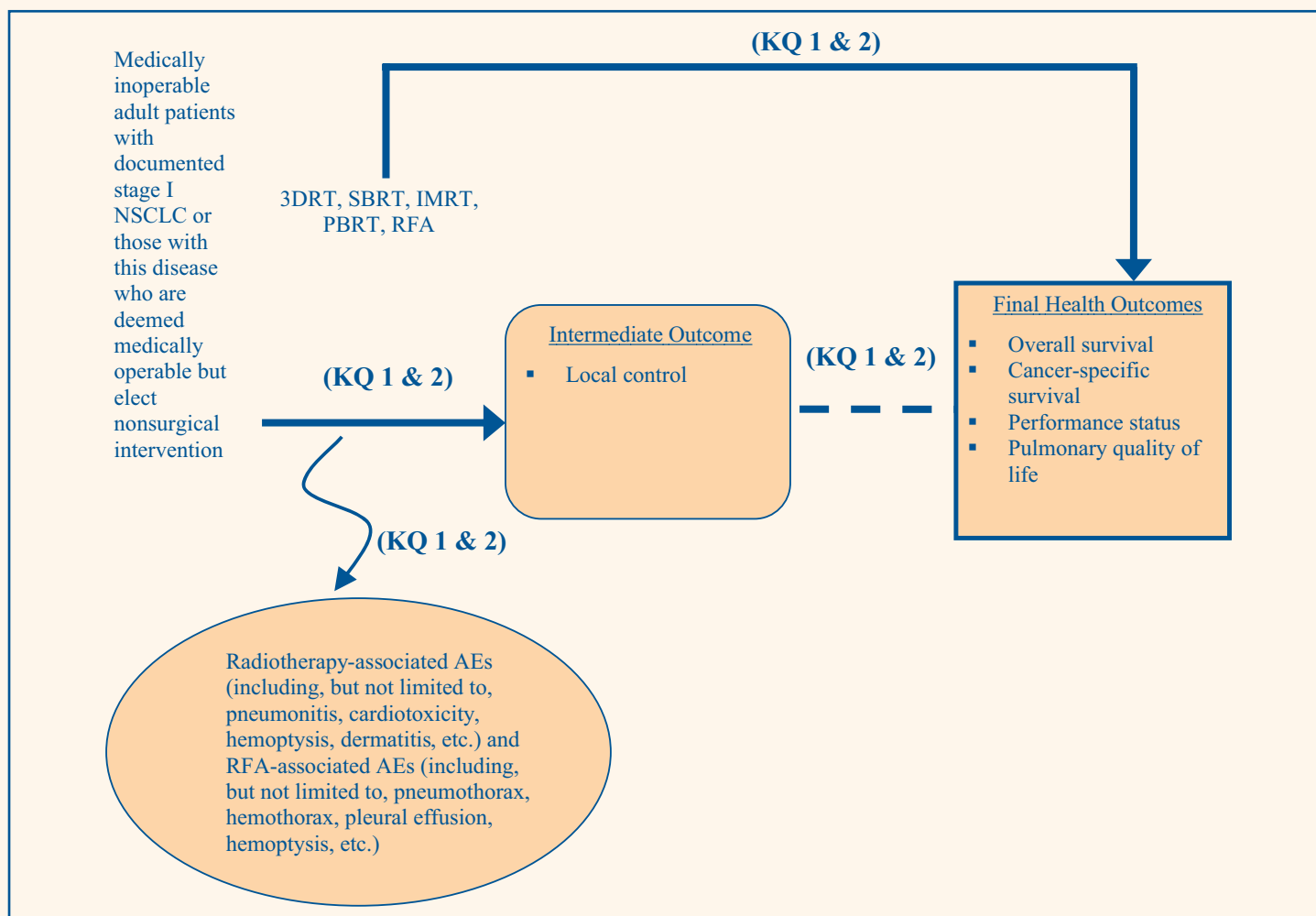
Methods

Input From Stakeholders

The topic for this report came via the Effective Health Care Program Web site. Initially a panel of Key Informants recruited by the Evidence-based Practice Center (EPC) gave input on draft Key Questions. The draft Key Questions were posted on AHRQ’s Web site for public comment on October 5, 2011, for 4 weeks. During this period, the EPC drafted a protocol for the CER and recruited a Technical Expert Panel (TEP) that comprised individuals with clinical expertise in radiation oncology, thoracic surgery and surgical oncology, pulmonology, and general oncology. In response to the comments received and with TEP input, we eliminated a Key Question aimed at “technically inoperable” patients, and expanded the list of adverse events (AEs) we would attempt to capture for each intervention. These changes were documented in the final protocol for this report, which was posted on AHRQ’s Web site on February 22, 2012.

The TEP provided input throughout the development of the review but was not involved in subsequent evidence analysis or drafting the report.

Figure A. 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) medically inoperable NSCLC or those with documented stage I NSCLC who are deemed operable but decline surgery



3DRT = three-dimensional radiotherapy; AE = adverse event; IMRT = intensity-modulated radiotherapy; KQ = Key Question; NSCLC = non-small-cell lung cancer; PBRT = proton beam radiotherapy; RFA = radiofrequency ablation; SBRT = stereotactic body radiotherapy
 Note: T, N, and M refer to tumor, lymph node involvement, and metastasis in the TNM staging system.

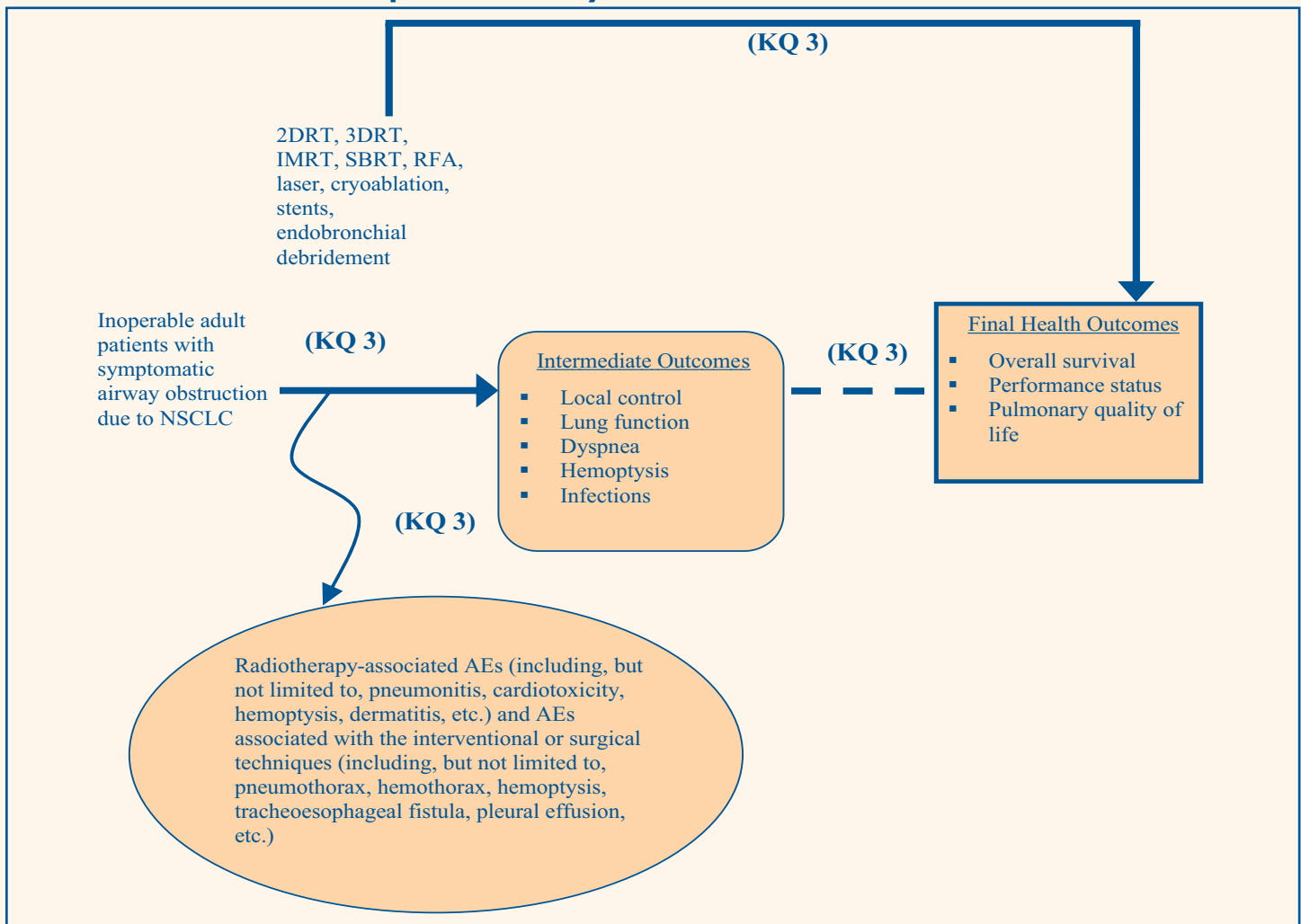
Data Sources and Selection

A medical librarian conducted electronic searches of MEDLINE®, Embase®, and the Cochrane Controlled Trials Registry, seeking randomized, nonrandomized comparative, and observational studies published between January 1, 1995, and July 25, 2012. We truncated the search at 1995 to ensure comparability of procedures and technologies. The search was limited to English-language studies based on the following rationale. First, evidence suggests that language restrictions do not change results of systematic review for conventional medical interventions.³⁰ 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 used the National Library of Medicine's Medical Subject Headings (MeSH®) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. The full search strings and strategies are listed in Appendix A of the full report.

We reviewed scientific information packets from the Scientific Resource Center and gray literature from the U.S. Food and Drug Administration Web site, ClinicalTrials.gov, and conference abstracts (American Society of Clinical Oncology and American Society for Radiation Oncology). We limited the gray literature to include only phase 3 randomized controlled trials (RCTs) through 2010. We did not contact study authors for unpublished results.

Figure B. Analytical framework for comparative effectiveness of local nonsurgical curative or palliative therapies for adult patients (age 18 years or older) with symptomatic inoperable airway obstruction due to NSCLC



2DRT = two-dimensional radiotherapy; 3DRT = three-dimensional radiotherapy; AE = adverse event; IMRT = intensity-modulated radiotherapy; KQ = Key Question; NSCLC = non-small-cell lung cancer; RFA = radiofrequency ablation; SBRT = stereotactic body radiotherapy

Inclusion Criteria

Studies of any design were included if they fulfilled all of the following inclusion criteria.

Key Questions 1 and 2

- Study included medically inoperable NSCLC stage I patients (T1N0M0 and T2N0M0) or medically operable NSCLC stage I patients (T1N0M0 and T2N0M0) who refuse surgery
- Such patients received only one of the following local nonsurgical interventions as first-line (definitive) treatment:
 - Conformal radiotherapy methods (including SBRT, 3DRT, IMRT)

– PBRT

– RFA

- Study reported ≥ 1 of the following types of outcome data for such patients:
 - Survival outcome (overall survival or cancer-specific survival)
 - Local control (an outcome defined as the arrest of cancer growth at the site of origin)
 - Pulmonary quality of life (QOL)
 - AEs specific to radiotherapy techniques or to RFA

Key Question 3

- Study included NSCLC patients of any stage with a symptomatic endoluminal obstruction

Table A. PICOTS for the Key Questions

PICOTS	Key Questions 1 and 2	Key Question 3
Population	<p>Key Question 1: Adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 and T2N0M0) NSCLC not deemed surgical candidates because of the documented presence of contraindications to major surgery—for example, cardiac insufficiency, poor pulmonary function, severe intercurrent illness, or poor performance status</p> <p>Key Question 2: Adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 and T2N0M0) NSCLC who would be deemed surgical candidates according to current clinical criteria but decline surgery</p>	Adult patients (age 18 years or older) with endoluminal NSCLC causing obstruction of the trachea, main stem, or lobar bronchi and recurrent or persistent thoracic symptoms such as hemoptysis, cough, dyspnea, and postobstructive pneumonitis who were treated with curative or palliative intent
Intervention	<p>All interventions are first-line (definitive), nonsurgical therapies:</p> <ul style="list-style-type: none"> • Conformal external-beam radiotherapy methods (including SBRT, 3DRT, and IMRT) • PBRT • RFA 	<ul style="list-style-type: none"> • Conventional 2DRT • Conformal PBRT methods (including SBRT, 3DRT, and IMRT) • Brachytherapy • RFA • Cryoablation • Laser therapy • Endobronchial debridement and stents • PDT • Electrocautery • Combinations—for example, endobronchial debridement plus a stent compared with debridement alone or combination of 2DRT with brachytherapy compared with radiotherapy alone • Because systemic therapy (chemotherapy) is used with radiotherapy or local nonsurgical interventional methods in stage III or greater patients, we collected information on chemotherapy to use in categorizing and assessing outcomes to ensure that 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
Comparator	<ul style="list-style-type: none"> • Comparators comprise the interventions noted above 	<ul style="list-style-type: none"> • Comparators comprise the interventions noted above

Table A. PICOTS for the Key Questions (continued)

PICOTS	Key Questions 1 and 2	Key Question 3
Outcome	<ul style="list-style-type: none"> Final health outcomes: OS, CSS, performance status, pulmonary QOL Intermediate outcomes: LCT Adverse outcomes: Radiotherapy-associated AEs (including, but not limited to, pneumonitis, cardiotoxicity, hemoptysis, dermatitis, etc.) and RFA-associated AEs (including, but not limited to, pneumothorax, hemothorax, hemoptysis, pleural effusion, etc.) 	<ul style="list-style-type: none"> Final health outcomes: OS, performance status, pulmonary QOL Intermediate outcomes: LCT, lung function, pulmonary symptoms (e.g., dyspnea, hemoptysis), respiratory tract infection Adverse outcomes: Radiotherapy-associated AEs (including, but not limited to, pneumonitis, cardiotoxicity, hemoptysis, dermatitis, etc.) and AEs associated with the interventional or surgical techniques (including, but not limited to, pneumothorax, pleural effusion, hemoptysis, transesophageal fistula, pericardial effusion)
Timing	<ul style="list-style-type: none"> The relevant periods occur from the time of treatment through followup over months (palliation) or years (OS) 	<ul style="list-style-type: none"> The relevant periods occur from the time of treatment through followup over months (palliation) or years (OS)
Setting	<ul style="list-style-type: none"> Inpatient and outpatient 	<ul style="list-style-type: none"> Inpatient and outpatient

2DRT = two-dimensional radiotherapy; 3DRT = three-dimensional radiotherapy; AE = adverse event; CSS = cancer-specific survival; IMRT = intensity-modulated radiotherapy; LCT = local control; NSCLC = non–small-cell lung cancer; OS = overall survival; PBRT = proton beam radiotherapy; PDT = photodynamic therapy; PICOTS = population, intervention, comparator, outcome, timing, and setting; QOL = quality of life; RFA = radiofrequency ablation; SBRT = stereotactic body radiotherapy

Note: T, N, and M refer to tumor, lymph node involvement, and metastasis in the TNM staging system.

- Such patients received ≥ 1 of the following local nonsurgical interventions:
 - Conformal radiotherapy methods (including SBRT, 3DRT, IMRT)
 - Conventional 2DRT
 - PBRT
 - RFA
 - Brachytherapy
 - Cryoablation
 - Laser therapy, including PDT
 - Electrocautery
 - Endobronchial debridement and stents
- Study reported data ≥ 1 of the following types of outcome data for such patients:
 - Survival outcome (overall survival or cancer-specific survival)
 - Local control (an outcome defined as the arrest of cancer growth at the site of origin)
 - Symptom relief
 - Pulmonary QOL

- AEs specific to radiotherapy or interventional techniques (e.g., RFA, cryoablation, electrocautery) or to surgical techniques (laser or mechanical debridement and stents)

Exclusion Criteria

- Editorials, commentaries, abstracts, animal studies, case reports, non–English-language, and diagnostic accuracy studies were excluded.
- Primary studies published prior to January 1, 1995, were excluded.
- If we identified more than one article that included the same patients, interventions, and outcomes, we included the article with the longest followup, excluding the earlier paper(s). The latter were cross-indexed in the abstraction tables.
- For Key Questions 1 and 2, we compared single interventions—for example, two different conformal radiotherapy methods, or RFA compared with a conformal radiotherapy method. We excluded studies that used any postintervention systemic (e.g., chemotherapy) or local nonsurgical therapy but did not define the therapy or disaggregate the clinical outcomes of such patients. Failure to stratify or disaggregate outcome data according to the treatment

received—for example, a local nonsurgical intervention with subsequent chemotherapy at progression—precludes determining whether an outcome such as overall survival could be attributed to the local intervention, the chemotherapy, or the combined effect of both therapies.

The list of excluded studies and reason for exclusion are provided in Appendix B of the full report.

Data Abstraction and Quality Assessment

Electronic search results were transferred to EndNote® and subsequently into DistillerSR® for study screening and selection. Using the study selection criteria outlined above for screening titles and abstracts, each citation was marked as: (1) eligible for review as full-text article or (2) ineligible for full-text review. Teams consisted of one senior member (the team leader) and two junior members. All team members initially examined at least one training set (n=100) of representative titles and abstracts for each Key Question to assure uniform application of screening criteria. They assessed a subsequent set, establishing concordance among the team. All team members performed title and abstract screening. A reference was excluded only when the senior and either junior team member made a concordant decision to exclude it. In case of disagreement between junior members, the team leader adjudicated in consensus discussion with all team members. A record of the reason for exclusion of each reference retrieved was kept in the DistillerSR database. A reference could be excluded for multiple reasons but only one reason was recorded.

A data abstraction guide was created that detailed the process and defined key data elements to ensure accuracy and consistency in the data abstraction procedure across the team. Junior and senior team member evaluated a test set of three references relevant to the three Key Questions to ensure that selection criteria were applied correctly. Subsequently, two junior team members and the team leader reviewed full-text articles independently to determine their inclusion in the systematic review. Team meetings were held regularly to discuss progress and to ensure that the team leader was aware of difficulties or problems in this process.

The main data elements for the CER were abstracted directly into Microsoft Word® tables. Other elements and the study risk-of-bias assessments were abstracted in DistillerSR. The evidence tables were divided by Key Question and assigned for abstraction to all team members. One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second

reviewed the articles and evidence tables for accuracy. Disagreements were resolved by discussion, and if necessary, by consultation with a third reviewer.

In adherence with the Methods Guide,²⁹ the risk of bias of individual comparative studies was assessed by the U.S. Preventive Services Task Force (USPSTF) criteria.³¹ The quality of the abstracted studies was assessed by one reviewer and examined by the senior team member.

The quality of comparative studies was assessed on the basis of the following criteria:

- Initial assembly of comparable groups: adequate randomization, including concealment and equal distribution among groups of potential confounders (e.g., other concomitant care)
- Maintenance of comparable groups (including attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Equal, reliable, and valid measurements (including masking of outcome assessment)
- Clear definition of interventions
- Consideration of all important outcomes
- Analysis:
 - For RCTs: intention-to-treat, covariate adjustment
 - For cohort studies: adjustment for potential confounders

Comparative studies were rated according to one of three quality categories:

Good. Studies are graded “good” if they meet 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 was 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 was used 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 are not maintained throughout the study; unreliable or invalid measurement instruments are used or measures are not applied at all equally among groups; key confounders are given little or no attention; there is a lack of masked outcome assessment; and, for RCTs, intention-to-treat analysis is lacking.

The quality of the single-arm intervention studies was assessed by Carey and Boden criteria.³² These include eight criteria, as follows:

- Clearly defined study questions
- Well-described study population
- Well-described intervention
- Use of validated outcome measures
- Appropriate statistical analyses
- Well-described results
- Discussion and conclusion supported by data
- Acknowledgement of the funding source

We created thresholds for converting the Carey and Boden risk-assessment tool into the AHRQ format of standard quality ratings (good, fair, and poor). This allowed us to differentiate the quality of single-arm studies as good, fair, or poor. For a study to be ranked good quality, all eight Carey and Boden criteria mentioned above had to be met. For a fair quality assessment, seven of eight criteria had to be met. A study that met fewer than seven of eight criteria was rated as poor quality. The quality rankings for these studies can be found in Appendix C of the full report.

Data Synthesis and Analysis

Given the lack of appropriate comparative studies for all Key Questions, this evidence review did not incorporate formal data synthesis involving meta-analysis. The quality of individual studies was assessed as outlined in the preceding section, and the strength of evidence (SOE) for each Key Question was evaluated as follows.

Assessment of the Strength of Evidence

We graded the strength of the overall body of evidence for overall survival, symptom relief, quality of life, and harms. The system used for rating the strength of the overall body of evidence is outlined in the AHRQ Methods Guide²⁹ and based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.³³ We also used

the GRADE guideline on assessing the risk of bias.³⁴ This system explicitly addresses four required domains: risk of bias, consistency, directness, and precision. Two independent reviewers rated all studies on domain scores and resolved disagreements by consensus discussion; the same reviewers also used the domain scores to assign an overall SOE grade.

The process of grading the body of evidence³³ was as follows. A body of evidence represented by RCT(s) would have a starting strength of high. A body of evidence represented by nonrandomized comparative studies would generally have a starting strength of low. For all study designs, the strength of evidence would be reduced by one level if there was high risk of bias, inconsistency or unknown consistency, indirectness, and imprecision. Further, based on GRADE guidelines on assessing the risk of bias,³⁴ when the evidence was generated from studies that had very serious risk of bias, the strength of evidence was rated down by two levels. Case series or single-arm studies were deemed indirect, imprecise, and “unknown” for the domains of directness, precision, and consistency.

The grade of evidence strength was 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 was either unavailable or did not permit estimation of an effect.

Additional domains, including strength of association, publication bias, coherence, dose-response relationship, and residual confounding, were not addressed in this review.

Results

Overview

Of the 4,648 unique titles identified, we screened 1,178 in full text. Of these, 55 met the CER inclusion criteria; 35 were relevant to Key Question 1, 6 were relevant to

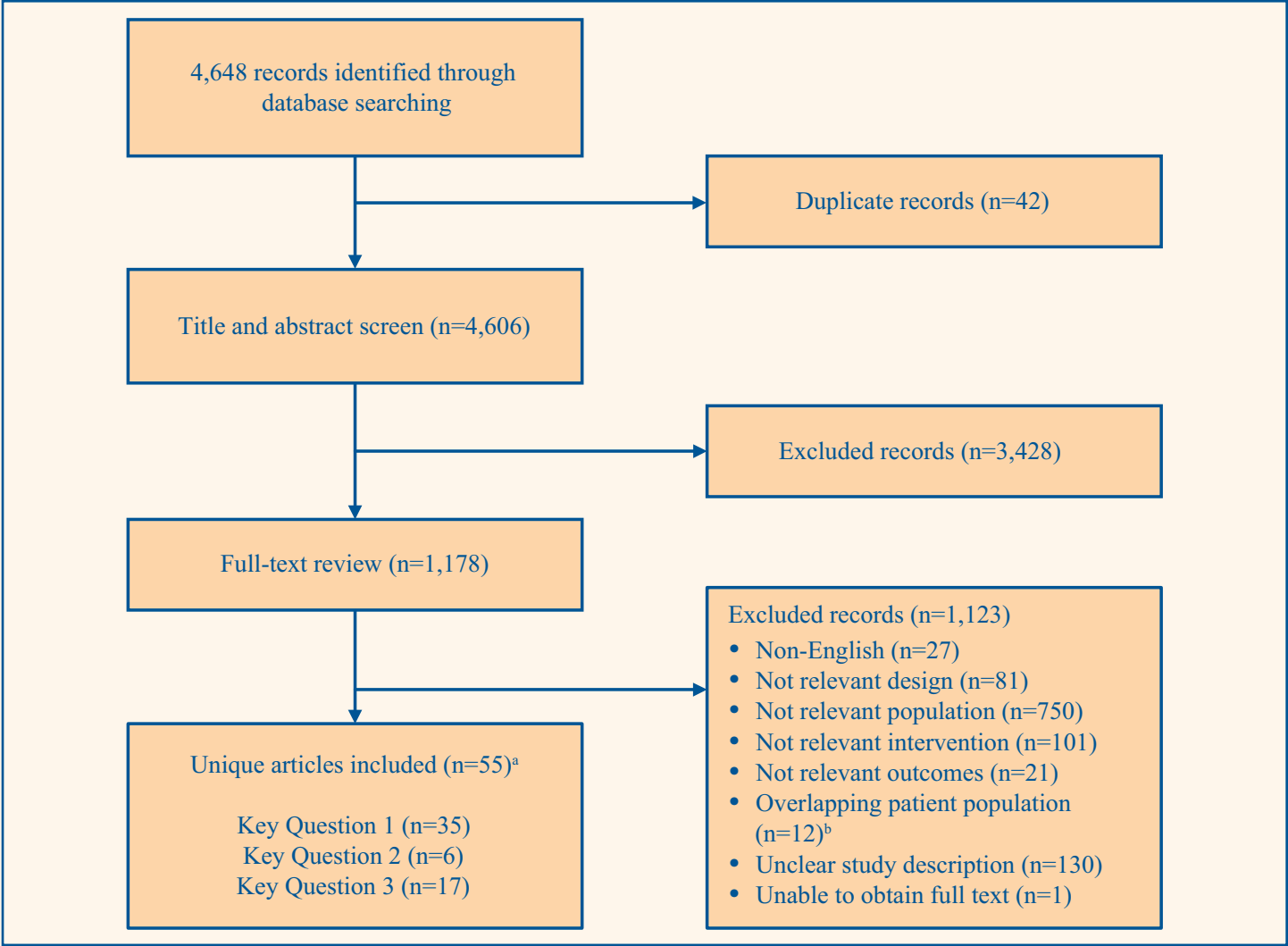
Key Question 2, and 17 were relevant to Key Question 3. Three studies addressed both Key Questions 1 and 2. Details are given in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)³⁵ diagram (Figure C). All studies relevant to Key Questions 1 and 2 were single-arm design, prospective (n=15), retrospective (n=21), or not specified (n=2). Among 17 papers included for Key Question 3, 5 were RCTs, 1 was a nonrandomized comparative study, and 11 were single-arm studies.

Key Points

Key Question 1: Comparative Effectiveness of Local Nonsurgical Definitive Interventions for Stage I NSCLC in Medically Inoperable Patients

- All evidence included in this report for Key Question 1 is from single-arm studies. No evidence is available from any type of direct comparative study of one intervention versus another.

Figure C. PRISMA diagram for disposition of literature search results



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

^aThree studies addressed both Key Questions 1 and 2.

^bOverlapping patient population refers to the studies in which the same patients were included in more than 1 study. In all such cases, only 1 study was included to avoid oversampling. The decision to include a study was based on the nature of the study design (preference of randomized controlled trials over observational study designs) and the clarity in reporting relevant patients and/or outcomes.

- Evidence from 35 single-arm studies is insufficient to form conclusions about the comparative benefits or harms of SBRT (24 reports), 3DRT (7 reports), PBRT (3 reports), or RFA (1 report) in medically inoperable patients with stage I NSCLC.
- The results of interest for this report comprise direct outcomes (overall survival and cancer-specific survival), an indirect outcome (local control), and radiation-associated toxicities, as shown in Figure A.
- Post-treatment toxicities were reported across studies, but no relative trend was detected among interventions.
- We are uncertain whether the limited evidence on AEs reflects that they were absent or that the investigators did not systematically collect data or report them.

Key Question 2: Comparative Effectiveness of Local Nonsurgical Definitive Interventions for Stage I NSCLC in Medically Operable Patients

- All evidence included in this report for Key Question 2 is from single-arm studies. No evidence is available from any type of direct comparative study of one intervention versus another.
- Evidence from six single-arm studies is insufficient to form conclusions about the comparative benefits or harms of SBRT (five reports) or PBRT (one report) in medically operable patients with stage I NSCLC.
- The results of interest for this report comprise direct outcomes (overall survival and cancer-specific survival), an indirect outcome (local control), and radiation-associated toxicities, as shown in Figure A.
- Post-treatment toxicities were not common across studies. No relative trend was detected among interventions.
- We are uncertain whether the limited evidence on AEs reflects that they were absent or that the investigators did not systematically collect data or report them.

Key Question 3: Comparative Effectiveness of Local Nonsurgical Therapies for Symptoms Secondary to an Inoperable Obstructive Endoluminal NSCLC

- All six RCTs included in this report were of poor quality according to the USPSTF rating criteria. Further analysis is provided in the Discussion section that follows.
- Evidence from six comparative studies is insufficient to draw conclusions about relative benefits and harms

of six unique treatment comparisons (brachytherapy plus EBRT vs. brachytherapy alone, brachytherapy plus EBRT vs. EBRT alone, brachytherapy vs. EBRT, laser plus brachytherapy vs. laser alone, laser vs. electrocautery, and laser vs. PDT) for local nonsurgical therapies in symptomatic inoperable patients with obstructive endoluminal NSCLC. Evidence from three single-arm studies of debridement and stenting is insufficient to draw conclusions about the effectiveness of those interventions.

- The results of interest for this report comprise direct outcomes (overall survival), symptom relief (cough, dyspnea, hemoptysis), and AEs (radiation toxicities, other intervention-associated AEs), as shown in Figure B.
- Overall, treatment-related toxicities varied according to the type of intervention. Hemoptysis was the most common toxicity reported across studies. There may be underreporting of treatment-related toxicities, as three comparative studies did not describe the frequency, process of data collection, or assessment of severity of treatment-related toxicities.

Discussion

Strength of Evidence

To evaluate the SOE, we used an approach that was specifically developed by the EPC program and referenced in the Methods Guide.²⁹ This approach is based on a system developed by the GRADE Working Group.³³ It explicitly addresses four required domains: risk of bias, consistency, directness, and precision, as outlined in the Methods section.

Key Question 1

As shown in Table B, the overall SOE is insufficient to form conclusions about the comparative beneficial effects or toxicities of 3DRT, PBRT, RFA, or SBRT in the treatment of stage I NSCLC in medically inoperable patients. Direct outcomes of interest were overall survival, cancer-specific survival, and toxicities.

Thirty-five single-arm studies were available. The risk of bias was high. The consistency of effect size direction is unknown in the absence of comparative studies. No direct comparative evidence is available among interventions, but the outcomes reported are direct. Precision cannot be determined in the absence of direct comparative evidence among interventions; therefore, the evidence was deemed imprecise.

Table B. Strength of evidence for local nonsurgical interventions in medically inoperable stage I NSCLC patients

Treatment and Evidence Base	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence
SBRT (24 single-arm studies, total n=1,665 patients)	High	Unknown	Indirect	Imprecise	Insufficient
3DRT (7 single-arm studies, total n=240 patients)	High	Unknown	Indirect	Imprecise	Insufficient
PBRT (3 single-arm studies, total n=144 patients)	High	Unknown	Indirect	Imprecise	Insufficient
RFA (1 single-arm study, n=19 patients)	High	Unknown	Indirect	Imprecise	Insufficient

3DRT = three-dimensional radiotherapy; NSCLC = non–small-cell lung cancer; PBRT = proton beam radiotherapy; RFA = radiofrequency ablation; SBRT = stereotactic body radiotherapy

Key Question 2

As shown in Table C, the overall SOE is insufficient to form conclusions about the comparative beneficial effects or toxicities of PBRT or SBRT in the treatment of stage I NSCLC in medically operable patients. Direct outcomes of interest were overall survival, cancer-specific survival, and toxicities.

Six single-arm studies were available. The risk of bias was high. The consistency of effect size direction is unknown in the absence of comparative studies. No direct comparative evidence is available among interventions, but the outcomes reported are direct. Precision cannot be determined in the absence of direct comparative evidence among interventions; therefore, the evidence was deemed imprecise.

Key Question 3

Overall, the evidence from RCTs is insufficient to form conclusions about the benefits (symptom relief, survival) and harms (treatment-related toxicities) of local nonsurgical therapies (brachytherapy plus EBRT vs.

brachytherapy alone, brachytherapy plus EBRT vs. EBRT alone, brachytherapy vs. EBRT, laser plus brachytherapy vs. laser alone, laser vs. electrocautery, laser vs. PDT) in symptomatic inoperable patients with obstructive endoluminal NSCLC. The strength of evidence for the six included RCTs is summarized in Table D.

Evidence from three single-arm studies of debulking and stenting is insufficient to draw conclusions about the effectiveness of those interventions. The SOE for the noncomparative studies included in the report is summarized in Table E.

Brachytherapy Plus EBRT Versus Brachytherapy Alone

The evidence for this comparison comprised one small RCT³⁶ (n=45, 15 patients per treatment arm). This trial was considered to have a high risk of bias because it failed to provide details of randomization and allocation concealment. The consistency of the evidence was unknown, as it was a single RCT without confirmation from any other study. The outcomes measured in the study—symptom relief, QOL and treatment-related toxicities—were all direct. The evidence for symptom

Table C. Strength of evidence for local nonsurgical interventions in medically operable stage I NSCLC patients

Treatment and Evidence Base	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence
SBRT (5 single-arm studies, total n=378)	High	Unknown	Indirect	Imprecise	Insufficient
PBRT (1 single-arm study, n=28)	High	Unknown	Indirect	Imprecise	Insufficient

NSCLC = non–small-cell lung cancer; PBRT = proton beam radiotherapy; SBRT = stereotactic body radiotherapy

relief, QOL, and treatment-related toxicities was imprecise.

Because the evidence base that addressed these outcomes consisted of an RCT, the starting level of SOE was high. SOE was reduced by one level each based on the high risk of bias, unknown consistency, and imprecision. Therefore, the SOE is insufficient that, compared with brachytherapy alone, brachytherapy plus EBRT improves symptom relief and QOL and reduces treatment-related toxicities.

Brachytherapy Plus EBRT Versus EBRT Alone

The evidence for this comparison comprised one small RCT³⁷ (n=95). This trial was considered to have a high risk of bias, primarily because the trial was discontinued prematurely due to lack of patient accrual and was underpowered to detect a difference in the rate of the primary endpoint (rate of dyspnea). The consistency of the evidence was unknown, as it was a single RCT without confirmation from any other study. The outcomes measured in the study—symptom relief, survival, and treatment-related toxicities—were all direct. The evidence for symptom relief, survival, and treatment-related toxicities was imprecise.

Because the evidence base that addressed these outcomes consisted of an RCT, the starting level of SOE was high. SOE was reduced by one level each based on the high risk of bias, unknown consistency, and imprecision. Therefore, the SOE is insufficient that, compared with EBRT alone, brachytherapy plus EBRT improves symptom relief and survival and reduces treatment-related toxicities.

Brachytherapy Versus EBRT

The evidence for this comparison comprised one small RCT³⁸ (n=99). This trial was considered to have a very serious risk of bias because the study failed to adjust for potential confounding resulting from crossover of a large proportion of patients between treatment arms during the trial period. The consistency of the evidence was unknown, as it was a single RCT without confirmation from any other study. The outcomes measured in the study—symptom relief, survival, and treatment-related toxicities—were all direct. The evidence for symptom relief and treatment-related toxicities was imprecise, while the evidence for survival was precise.

Because the evidence base that addressed these outcomes consisted of an RCT, the starting level of SOE was high. SOE was reduced by two levels based on very serious risk of bias, by one level for unknown consistency, and by one level for imprecision (only for symptom relief and treatment toxicity). Therefore, the SOE is insufficient that,

compared with EBRT, brachytherapy improves symptom relief and survival and reduces treatment-related toxicities.

Laser Plus Brachytherapy Versus Laser Alone

The evidence for this comparison comprised one small RCT³⁹ (n=29). This trial was considered to have a high risk of bias, primarily due to failure to provide details of randomization, allocation concealment, and NSCLC staging of patients at the baseline. The consistency of the evidence was unknown, as it was a single RCT without confirmation from any other study. The outcomes measured in the study—symptom relief, survival, and treatment-related toxicities—were all direct. The evidence for symptom relief, survival, and treatment-related toxicities was imprecise.

Because the evidence base that addressed these outcomes consisted of an RCT, the starting level of SOE was high. SOE was reduced by one level each based on the high risk of bias, unknown consistency, and imprecision. Therefore, the SOE is insufficient that, compared with laser alone, laser plus brachytherapy improves symptom relief and survival and reduces treatment-related toxicities.

Laser Versus PDT

The evidence for this comparison comprised one small RCT⁴⁰ (n=31). This trial was considered to have a serious risk of bias, primarily because the treatment arms had imbalances at the baseline. The proportion of patients with stage III–IV cancer was much smaller in the PDT group (57%, 8 of 14) than the laser group (88%, 15 of 17) at the baseline. The consistency of the evidence was unknown, as it was a single RCT without confirmation from any other study. The outcomes measured in the study—survival and treatment-related toxicities—were all direct. The evidence for treatment-related toxicities was imprecise, while it was precise for survival.

Because the evidence base that addressed these outcomes consisted of an RCT, the starting level of SOE was high. SOE was reduced by two levels based on very serious risk of bias, by one level for unknown consistency, and by one level for imprecision (only for treatment-related toxicity). Therefore, the SOE is insufficient that, compared with photodynamic therapy, laser therapy improves survival and reduces treatment-related toxicities.

Laser Versus Electrocautery

The evidence for this comparison comprised one small nonrandomized comparative study⁴¹ (n=29). This study was considered to have serious risk of bias, primarily because of lack of adjustment for any potential confounders. A disproportionate number of patients

had received previous treatment in the laser-treated group (93%) compared with the electrocautery group (53%). Further, the mean time from diagnosis to study treatment was different in the two groups (4.7 months in the laser group vs. 7.5 months in the electrocautery group). The consistency of the evidence was unknown, as it was a single nonrandomized comparative study without confirmation from any other study. The outcomes measured in the study—survival and symptom relief—were direct. The evidence for symptom relief and survival was imprecise.

Because the evidence base that addressed these outcomes consisted of a nonrandomized comparative study, the starting level of SOE was low. SOE was reduced by two

levels based on very serious risk of bias and by one level each for unknown consistency and imprecision. Therefore, the SOE is insufficient that, compared with electrocautery, laser therapy improves survival and symptom relief.

Applicability of the Findings

Our results show no direct comparative evidence to support a decision among 3DRT, PBRT, RFA, or SBRT in stage I NSCLC patients. Comparative evidence is sparse among any of the interventions considered in Key Question 3. In the absence of direct comparative effectiveness data, additional factors may be considered in making a treatment decision. Those could include relative convenience and cost, issues outside the scope of this CER.

Table D. Strength of comparative evidence for local nonsurgical therapies for symptoms secondary to an inoperable obstructive endoluminal NSCLC

Treatment and Evidence Base	Outcome	Unit of Measure	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence
Brachytherapy plus EBRT vs. brachytherapy alone (1 RCT, n=45)	Symptom relief	Incidence and response rate	High	Unknown	Direct	Imprecise	Insufficient
	QOL	EORTC QLQ-C30 & LC 13 V3.0 instruments					
	Treatment toxicity	Incidence of Grade \geq II RTOG morbidity scoring criteria					
Brachytherapy plus EBRT vs. EBRT alone (1 RCT, n=95)	Symptom relief	Response rate	High	Unknown	Direct	Imprecise	Insufficient
	Survival	Overall survival					
	Treatment toxicity	Incidence					
Brachytherapy vs. EBRT (1 RCT, n=99)	Symptom relief	% improvement	High	Unknown	Direct	Imprecise	Insufficient
	Survival	Overall survival	High	Unknown	Direct	Precise	Insufficient
	Treatment toxicity	Incidence	High	Unknown	Direct	Imprecise	Insufficient
Nd-YAG plus brachytherapy vs. Nd-YAG alone (1 RCT, n=29)	Symptom relief	Speiser's index	High	Unknown	Direct	Imprecise	Insufficient
	Survival	Overall survival					
	Treatment toxicity	Overall survival					
Photodynamic therapy vs. laser (1 RCT, n=31)	Survival	Overall survival	High	Unknown	Direct	Precise	Insufficient
	Treatment toxicity	Incidence	High	Unknown	Direct	Imprecise	Insufficient
Nd-YAG vs. electrocautery (1 NRC, n=29)	Survival	Mean survival	High	Unknown	Direct	Imprecise	Insufficient
	Symptom relief	% response					

EBRT = external-beam radiotherapy; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; Nd-YAG = neodymium-doped yttrium aluminum garnet; NRC = nonrandomized comparative study; NSCLC = non-small-cell lung cancer; QOL = quality of life; RCT = randomized controlled trial; RTOG = Radiation Therapy Oncology Group

Table E. Strength of noncomparative evidence for local nonsurgical therapies for symptoms secondary to an inoperable obstructive endoluminal NSCLC

Treatment and Evidence Base	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence
RFA (1 study, n=33)	High	Unknown	Indirect	Imprecise	Insufficient
BT + STNT (1 study, n=10)	High	Unknown	Indirect	Imprecise	Insufficient
LASR + STNT (1 study, n=52)	High	Unknown	Indirect	Imprecise	Insufficient

BT = brachytherapy; LASR = laser; NSCLC = non-small-cell lung cancer; RFA = radiofrequency ablation; STNT = stenting

Key Questions 1 and 2

In general, applicability assessment would depend on a body of evidence sufficient to permit conclusions about the comparative outcomes of local nonsurgical therapies for stage I NSCLC. The evidence for Key Questions 1 and 2 does not reach that level, so we have primarily limited comments to the relevance of the PICOTS elements. The PICOTS format is a practical and useful structure to review applicability in a systematic manner. With the exception of cost, factors potentially affecting the applicability of the findings of this CER are summarized in Table F for Key Questions 1 and 2.

The degree to which the data presented in this report are applicable to clinical practice is a function of the similarity between populations in the included studies and the patient population that receives clinical care in diverse settings. It also is related to the relative availability of the interventions. The literature base is observational, lacking comparative evidence. Case series are descriptive studies that are limited in their ability to control for biases. Selection bias is of particular concern, as patients receive treatment based on clinician preferences, center resources, and patient characteristics and preference rather than random allocation. This evidence base is therefore insufficient to support any attempt to draw comparative conclusions.

Key Question 3

Multiple shortcomings of the current evidence base for Key Question 3 preclude interpretation about general applicability. First, the comparative benefits and harms of various endobronchial treatments are still unknown because of the lack of good-quality RCTs. The available studies were all poor quality, and often were small and not powered to detect a prespecified clinically meaningful difference in a standardized outcome of interest. Second, patient characteristics were poorly defined. The majority of studies did not report performance status, and therefore it is difficult to assess the relative health and activity level of these patients and to whom this limited evidence applies. Third, there was a wide variation in the outcome

measures to report symptom relief in the current studies. Fourth, many studies did not report the frequency, process, or method of assessing severity of treatment-related toxicities, and therefore the true harms associated with these interventions are likely to be underrepresented in the current data. Some factors that affect applicability of the findings of this CER are summarized in Table G for Key Question 3.

Findings in Relationship to What Is Already Known

We sought credible sources of evidence-based information on the use of the local interventions assessed in this CER to treat NSCLC. Our systematic literature search and review revealed no relevant evidence-based guidelines we could compare with our findings for Key Questions 1 and 2, and two publications relevant to Key Question 3.^{27,42} Our report offers the first comprehensive systematic review on this topic.

Limitations of Current Review and Evidence Base

Key Questions 1 and 2

The primary limitation for Key Questions 1 and 2 is lack of comparative trials of any design. Percutaneous image-guided RFA has been investigated as an option for the treatment of stage I NSCLC. In our review, we found that RFA studies in lung primarily comprise heterogeneous case series that are complicated by several factors. First, many reports included metastatic and primary lesions from nonlung and lung sites, but did not stratify outcomes such as overall survival according to tumor stage or type. Second, the technical details of RFA, such as the type of equipment used, the power settings or wattage delivered, and details of followup assessment and subsequent therapy, were not consistent or consistently reported across studies. These factors conspired to severely limit RFA study selection in the report.

Although the body of evidence we included for the conformal radiotherapy techniques addressed in Key Questions 1 and 2, particularly SBRT, was more

Table F. Summary of applicability of evidence for Key Question 1 and Key Question 2

Domain	Applicability of Evidence
Populations	<ul style="list-style-type: none"> Overall, the patients included in the single-arm studies were not suitable for surgery or were suitable for surgery but declined it. Patients with stage I NSCLC in the studies included in this report appear to be representative of cases that would be considered for a local nonsurgical intervention. Patients typically were in their late 60s to mid-70s, congruent with the incidence of stage I NSCLC, which tends to rise with age. The medically inoperable patients of KQ1 had compromised cardiopulmonary reserves or other comorbidities that preclude surgical resection. The medically operable patients of KQ2 were often not substantially different from the inoperable population of KQ1, but neither group is considered as healthy as the population that undergoes surgery.
Interventions	<ul style="list-style-type: none"> 3DRT, IMRT, and SBRT represent different technological approaches to the delivery of conformal photon radiotherapy. The major advantage of these interventions compared with traditional wide-field 2DRT is the ability to deliver tightly focused cytotoxic radiation by delineating the shape and size of the tumor using a CT-based or other imaging planning system. 3DRT represents a minimum technical standard for delivery of conformal radiotherapy. It involves static fields with a fixed shape, modified by compensators (wedges and segments). 3DRT is widely available. IMRT offers beam strength attenuation through a multileaf collimator (tungsten), with dynamic field shapes for each beam angle. IMRT is not as widely available as 3DRT and requires a higher level of inverse planning effort and quality assurance. SBRT is a hypofractionated technique administered in 5 or fewer fractions; 3DRT and IMRT typically deliver radiation in many more fractions than SBRT. SBRT is not as widely available as 3DRT or IMRT, but its use is growing. It may soon supplant other technologies in the KQ1 and KQ2 settings. The institutional programmatic requirements for SBRT are similar to those for IMRT. This CER did not allow for a rigorous and systematic comparison of the relative performance of local nonsurgical therapies stratified by technological factors. The impact of these factors on health outcomes remains unclear. Applicability of the evidence for PBRT and RFA is unknown due to limited evidence.
Comparators	<ul style="list-style-type: none"> See above for Interventions.
Outcomes	<ul style="list-style-type: none"> The major beneficial health outcomes in this CER are OS, CSS, and LCT, typically reported over a period of 1 to 5 years. OS is the primary direct outcome for any cancer intervention study. CSS reflects the absolute effect of a cancer intervention on the disease. CSS is a highly relevant direct outcome in the KQ1 practice setting, in that such patients are generally fragile and susceptible to succumbing to underlying comorbidities. Its relevance in KQ2 patients may be slightly less than in KQ1, as the former may be relatively healthier than the latter, but they still are not as healthy as good surgical candidates. LCT is of interest to patients because it measures the effectiveness of an intervention in disease control. Upon local failure, patients enter into a new category centered on systemic chemotherapy. This is a potentially perilous position for the medically frail patients considered in KQ1, and perhaps many of those in KQ2.
Timing	<ul style="list-style-type: none"> The relevant periods occur from the time of treatment through followup over months (palliation) or years (overall survival).
Setting	<ul style="list-style-type: none"> The evidence for KQ1 and KQ2 is international, primarily obtained in tertiary institutional settings. More sophisticated interventions such as IMRT and SBRT require an institutional commitment to quality assurance and ongoing training that may be difficult to achieve in smaller community-based centers. We did not collect or analyze information to examine these issues.

2DRT = two-dimensional radiotherapy; 3DRT = three-dimensional radiotherapy; CER = Comparative Effectiveness Review; CSS = cancer-specific survival; CT = computer tomography; IMRT = intensity-modulated radiotherapy; KQ = Key Question; LCT = local control; NSCLC = non-small-cell lung cancer; OS = overall survival; PBRT = proton beam radiotherapy; RFA = radiofrequency ablation; SBRT = stereotactic body radiotherapy

Table G. Summary of applicability of evidence for Key Question 3

Domain	Applicability of Evidence
Populations	<ul style="list-style-type: none"> The patients in the studies included in this report appear to be representative of cases that would be considered for a bronchoscopic intervention. All patients included in the 6 studies had histologically confirmed NSCLC with airway obstruction that required a bronchoscopic intervention. The mean age of patients included in these studies ranged from 61 to 68 years, and this is congruent with the incidence of NSCLC, which tends to rise with age.
Interventions	<ul style="list-style-type: none"> The single-modality nonsurgical interventions (brachytherapy, EBRT, electrocautery, laser, photodynamic, debridement, and stenting) and 2 dual-modality interventions (laser plus brachytherapy and brachytherapy plus EBRT) represent a general landscape of current treatment options for patients with endoluminal obstructive NSCLC and therefore are applicable.
Comparators	<ul style="list-style-type: none"> See above for Interventions.
Outcomes	<ul style="list-style-type: none"> The major outcomes of interest were symptom relief, OS, disease-specific survival, QOL, and treatment-related toxicity. Although OS is the primary direct outcome for any cancer intervention study, it may not be the best measure of the efficacy of a palliative intervention in symptomatic patients. Immediate relief of obstructive symptoms and improvement in QOL provide reasonable and pertinent justification for use of endobronchial intervention in such patients. According to the structured review by the Patient Reported Outcome Measurement Group- Oxford on the use of PROMs (Patient Reported Outcome Measures), both generic and disease-specific instruments exist that can be used in patients with lung cancer to assess the impact of interventions on QOL. These measures include generic measures such as SF-36 and EQ-5D and lung cancer-specific measures such as the EORTC QLQ-C30 and EORTC QLQ-LC13 instruments, and FACT-L. However, QOL data were reported only by 1 small study out of the 6 comparative studies. Therefore, the applicability of the current evidence base on QOL cannot be determined.
Timing	<ul style="list-style-type: none"> The relevant periods occur from the time of treatment through followup over months (palliation) or years (overall survival).
Setting	<ul style="list-style-type: none"> The outcomes of local bronchoscopic therapies largely depend on the expertise of the provider and the center providing these services. We could not assess the impact of such operating characteristics on the treatment outcomes because these data were not available in the published papers.

EBRT = external beam radiotherapy; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D = EuroQOL 5 dimension; FACT-L = Functional Assessment of Cancer Therapy- Lung; NSCLC = non-small-cell lung cancer; OS = overall survival; QOL = quality of life; SF-36 = Short Form 36 Health Survey

substantial in quantity than the evidence for RFA, we have similar concerns about interstudy heterogeneity, with variability in radiotherapy dose, schedule of treatment, patient selection criteria, tumor size and location, and so forth. In a systematic review in general, heterogeneous noncomparative evidence makes it very difficult to assess the benefits and harms of any intervention. In this CER, the type of evidence we identified for Key Questions 1 and 2 precludes comparative assessment among the interventions we investigated. We therefore believe further careful study of the interventions we considered in this CER is needed in the settings of Key Question 1 or 2 to establish optimal technical protocols and patient selection criteria, perhaps standardizing and comparing them across institutions. These data and methods could, in theory, be applied to the design and conduct of comparative studies of the local nonsurgical interventions for stage I NSCLC, as outlined in the Research Gaps section below.

Key Question 3

The body of evidence available for Key Question 3 comprised five RCTs, one nonrandomized comparative study, and three relevant single arms from three otherwise comparative studies. We included the latter three study arms because we did not have higher level evidence for the interventions in question, debridement and stenting. Significant limitations in the quality and quantity of the evidence base led us to conclude that the evidence was insufficient to make conclusions about the comparative effectiveness of local nonsurgical interventions to treat endobronchial obstructions in NSCLC patients. There was only one comparative study available to draw inferences about comparative effectiveness for six unique treatment comparisons. Therefore, the consistency domain for SOE was unknown. All six studies received a low rating in terms of USPSTF study quality; often the studies were small and not powered to detect a prespecified

clinically meaningful difference in a standardized outcome of interest, thereby limiting their utility beyond hypothesis generation. Most studies lacked details about randomization and allocation concealment. The one nonrandomized comparative study available for Key Question 3 did not use statistical adjustment to reduce confounding; such adjustment for confounding should be consistently used in nonrandomized studies.

Research Gaps

Key Questions 1 and 2

The primary research gap we identified in preparing this CER is the lack of evidence from comparative studies to draw conclusions as to the relative clinical benefits and harms of the local nonsurgical interventions used in the stage I NSCLC setting of medically inoperable or operable patients. We also identified some feasibility issues associated with the interventions that are potential impediments to the type of rigorous comparative studies we suggest are necessary to determine their comparative effectiveness. In this section, we first describe characteristics of ideal comparative studies we believe are needed to compare these technologies. Some potential impediments to such studies are discussed subsequently in this section.

Lack of Clinical Trial Evidence on Local Nonsurgical Interventions for Stage I NSCLC

As part of this review, we searched for ongoing clinical trials of these technologies in stage I NSCLC. In the process, we identified two international randomized phase 3 clinical trials of surgical resection versus SBRT that are recruiting patients (NCT 01336894 and NCT 00840749). However, neither of these trials will reveal relative outcomes among local nonsurgical interventions in stage I NSCLC. Thus, we suggest that prospective studies are needed to properly evaluate the relative clinical benefits and harms of the technologies evaluated in this CER, taking into account the potential impediments to study we discuss below. Ideally, comparative studies in medically inoperable or operable stage I NSCLC patients would incorporate the following:

- To assure comparability of patients and minimize bias, standardized patient selection criteria would be used that involve consultation, including a thoracic surgeon, medical oncologist, and radiation oncology specialist. Key factors to consider include comorbidity status (particularly cardiopulmonary function and capacity), age, performance status, tumor size, and tumor location.

- Standardized intervention protocols with training and quality assurance programs within and across participating institutions are necessary for the best study. For radiotherapy, key factors would include the imaging and planning method, immobilization method, dose and fractionation schedule, and the biologically effective dose (BED) for comparisons of different modalities (e.g., SBRT, 3DRT, IMRT, and PBRT). For RFA, issues would include treatment power and duration in the context of tumor size and location.
- Prespecified followup criteria and methods—in particular, notation of subsequent systemic therapy administered at recurrence—are key considerations. Subsequent systemic therapy is a key concern because it is impossible to discern the effect of an intervention followed by systemic therapy at progression from that achieved with the intervention alone. Is the effectiveness a function of the systemic therapy, the intervention, or the combination?
- Rigorous and standardized reporting is needed to account for all patients and treatments received. Data for operable and inoperable patients would be reported separately. We urge that rigorous methods be used for the conduct of RCTs, particularly intent-to-treat analysis and adjustment of survival data to account for patients who develop recurrent disease and subsequently receive systemic chemotherapy as part of their treatment plan.
- Primary outcomes would include overall survival, cancer-specific survival, and local control. Prespecified systematic collection of AEs using validated criteria (e.g., Common Terminology Criteria for Adverse Events [CTCAE]) is necessary to permit accurate assessment of relative benefits and risks of the interventions.

Potential Impediments to Comparative Studies of Local Nonsurgical Interventions for Stage I NSCLC

The general dissemination of conformal radiotherapy technologies into community clinical practice, most lately and specifically SBRT,^{43,44} is a potential impediment to comparative study of those technologies. Published survey results show that nearly 40 percent of solo practitioners already treat patients with SBRT, which suggests that this technology is accessible and its efficacy accepted in the broader radiation oncology community.^{43,44} The shorter hypofractionated SBRT course is more “patient friendly” than those associated with conventionally fractionated conformal radiotherapy methods. This patient-specific advantage may represent an additional

reason that SBRT has rapidly disseminated into clinical practice in the absence of direct comparative clinical trial evidence to support its reputation of clinical superiority over conventionally fractionated conformal techniques. We also recognize a number of other significant, perhaps insurmountable, technical impediments to conducting adequate comparative studies among the most widely available conformal radiotherapy-based modalities and other interventions such as RFA. These are outlined below.

Several practical limitations would complicate comparative study of RFA and conformal radiotherapy modalities in the stage I NSCLC setting. Although we did not evaluate these issues in this CER, it is generally thought that a tumor size greater than 4 cm or a tumor location less than 1 cm from the hilum or large vessels precludes the use of RFA.^{22,45} Current clinical wisdom suggests that RFA is best suited for patients with peripherally located, smaller lesions due to the “heat sink” effect of large blood vessels that dissipates heat from the tumor and reduces efficacy.⁴⁵⁻⁴⁷ By contrast, although we also did not investigate any relationship in our systematic review, conformal radiotherapy-based modalities, particularly SBRT, have been used in patients with either peripheral or central tumors, as well as tumors > 4 and up to 7 cm in diameter, the latter corresponding to stage IB (T2N0M0).⁴ Furthermore, radiotherapy-based modalities are not subject to a heat sink effect that limits their efficacy. Given those caveats, recruitment and accrual of sufficient numbers of well-matched stage I NSCLC patients to make meaningful, clinically relevant comparisons between RFA and conformal radiotherapy-based treatments could be difficult.

A key technical issue in comparing the radiotherapy interventions likely is the significant difference in the BED of radiation that can be safely delivered by SBRT compared with IMRT or 3DRT delivered with conventional fractionation protocols. In brief, radiation therapy for NSCLC typically is delivered to a total dose of 60-70 Gy; SBRT delivers that dose in three to five fractions of 20 Gy each (estimated BED = 180 Gy₁₀ using standard principles), whereas conventionally fractionated IMRT or 3DRT delivers 60-70 Gy in 30 fractions of 2 Gy each in 4 to 5 weeks, yielding an estimated BED of 72 Gy₁₀. The difference in attainable BED is considered to have potential efficacy implications.⁴⁸ The higher BED causes tumor ablation, rather than tumor cell kill, allowing for little to no tumor cell repopulation between doses of radiation.

In this CER, we did not systematically investigate whether a higher BED delivered by any conformal

radiotherapy modality can be associated with better clinical outcomes, such as overall survival, compared with a lower BED. This has been reported in published single-arm studies reviewed in this CER—for example, the large multicenter retrospective series on SBRT in Japan by Onishi and colleagues.⁴⁹ However, we are not aware of any direct comparative evidence on this topic for any of the conformal radiotherapy technologies, so it is not possible to make even indirect comparisons between the delivered BED and clinical outcomes in any case. Furthermore, we are aware of no published clinical trial evidence to ascertain whether a higher BED delivered by SBRT is associated with differences in patient outcomes compared with a lower BED delivered either by SBRT or by a conventionally fractionated conformal radiotherapy modality. We acknowledge that the difference in delivered BED has biologically plausible clinical implications, and perhaps ethical implications, that would need to be addressed in designing any type of study to compare conformal radiotherapy-based technologies. However, it is not clear to us that the BED issue under discussion here is settled.

In summary, we acknowledge the views of some members of the radiation oncology and interventional radiology communities that clinical trials of local nonsurgical modalities, including RFA, SBRT, and other conformal radiotherapy modalities (e.g., 3DRT, IMRT, PBRT), in stage I NSCLC patients may be very difficult to recruit and conduct, based on technical and potential ethical issues related to perceptions of unequal clinical benefit among the interventions. However, we maintain that current evidence is insufficient to support a view that clinical outcomes achieved with one technology are superior or inferior to those achieved with other modalities. Clinical evidence from comparative studies is needed to establish the standard of care for local nonsurgical treatment of stage I NSCLC patients.

Key Question 3

Lack of Clinical Trial Evidence on Local Nonsurgical Interventions for Endoluminal Obstructive NSCLC

- Key Question 3 compared outcomes of available local endobronchial interventions used with curative or palliative intent to treat airway obstruction as a result of NSCLC. Evidence on the patient outcomes is limited and, as such, is insufficient to make conclusions. We identified a number of research gaps during the course of review:
- Lack of comparative evidence generated from adequately powered RCTs regarding the benefits and

harms of various bronchoscopic interventions used for treating endoluminal obstructions in patients with NSCLC

- Lack of comparative evidence generated from good-quality RCTs regarding the QOL data from patients who receive various bronchoscopic interventions used for treating endoluminal obstructions in patients with NSCLC
- Need for systematic collection of treatment-related toxicity data from various bronchoscopic interventions used for treating endoluminal obstructions from actual clinical practice settings

During our review, we identified two RCTs that aimed to compare local endobronchial interventions in patients with endobronchial NSCLC. However, neither of these trials were completed due to lack of patient accrual. Of these two RCTs, the trial by Moghissi and colleagues⁵⁰ is notable. The objective of this trial was to compare two treatment policies in terms of symptom relief, respiratory function, performance status, QOL, and survival. This study planned to recruit 400 patients in 3 years at 24 clinical centers in the United Kingdom. Even though the study organizers had successfully conducted many RCTs in the past, they failed to recruit patients in this clinical setting. Moreover, 20 percent of those randomized did not receive the assigned treatment. A study by Langendijk and colleagues,³⁷ which randomized patients to a brachytherapy plus EBRT or EBRT-alone arm, was discontinued due to lack of patient accrual before completing the planned enrollment of 160 patients.

Potential Impediments to Comparative Studies of Local Nonsurgical Interventions for Endoluminal Obstructive NSCLC

NSCLC patients with endoluminal obstructions are particularly difficult to randomize in trials because of many reasons, particularly ethical issues. Most of these bronchoscopic interventions are considered complementary and are used sequentially in a clinical setting,⁵¹ and therefore randomizing critically ill patients to either therapy alone has ethical implications. Further, many of these patients present with an impending obstruction, and immediate symptom relief is foremost. Obtaining informed consent in such a situation is a barrier in patient recruitment. These reasons are likely to obviate successful conduct of a future RCT.

A prospective cohort study may be able to answer some questions about relative harms and benefits of

local endobronchial interventions. Although concerns about selection bias and unknown confounders always exist in such a study design, addressing and collecting data about most relevant confounders a priori can provide much-needed information about comparative benefits and harms of these therapies in the population of interest. We recommend that the research team for conducting such a study be multidisciplinary, including oncologists experienced in treating NSCLC patients with endobronchial obstruction, a methodologist with expertise in QOL measurement, clinical researchers with expertise in the planning and conduct of large cohort multicentric studies, and ethicists. Relevant outcomes that would be measured in such a study include symptom control, QOL, survival, and treatment-related AEs. Data related to symptom control would be captured using a standardized validated tool applied uniformly across all interventions. Generic instruments such as the Short Form 36 Health Survey (SF-36) and EuroQOL 5 dimension (EQ-5D) would be used in conjunction with lung cancer–specific measures such as European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) modules C30 and LC13 and Functional Assessment of Cancer Therapy-Lung (FACT-L) to measure QOL data.

Treatment-related AEs would be assessed from the date of the procedure extending to a reasonable time, preferably until death, using standardized and well-defined criteria with an independent causality analysis. The process to capture AEs that occur when patients are not under direct medical supervision (such as at home or in a long-term care facility) would also be prespecified in the study protocol. Data on all potential prognostic covariates would include, but not be limited to, patient characteristics (age, sex, race, performance status, comorbidities); disease characteristics (tumor stage, histopathology, location, size, blockage); and technical attributes of the procedure (technical success, technical variables related to use of procedures, type of instrument used) as well as data on the operator (expertise, years of experience, size of the facility).

Conclusions

Evidence is insufficient to permit conclusions on the comparative effectiveness of local nonsurgical therapies for inoperable or operable patients with stage I NSCLC or inoperable NSCLC patients with endoluminal tumor causing pulmonary symptoms. Important outcomes of therapy include overall survival, AEs, and QOL.

References

- Goldstraw P, Ball D, Jett JR, et al. Non-small-cell lung cancer. *Lancet*. 2011 Nov 12;378(9804):1727-40. PMID: 21565398.
- Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. *CA Cancer J Clin*. 2010 Sep-Oct;60(5):277-300. PMID: 20610543.
- Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol*. 2004 Jan 15;22(2):330-53. PMID: 14691125.
- Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. *Chest*. 2009 Jul;136(1):260-71. PMID: 19584208.
- Rankin SC. Staging of non-small cell lung cancer (NSCLC). *Cancer Imaging*. 2006;6:1-3. PMID: 16478697.
- Christie NA, Pennathur A, Burton SA, et al. Stereotactic radiosurgery for early stage non-small cell lung cancer: rationale, patient selection, results, and complications. *Semin Thorac Cardiovasc Surg*. 2008 Winter;20(4):290-7. PMID: 19251167.
- Crino L, Weder W, van Meerbeeck J, et al. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010 May;21 Suppl 5:v103-15. PMID: 20555058.
- Decker RH, Tanoue LT, Colasanto JM, et al. Evaluation and definitive management of medically inoperable early-stage non-small-cell lung cancer. Part 1: Assessment and conventional radiotherapy. *Oncology (Williston Park)*. 2006 Jun;20(7):727-36. PMID: 16841796.
- Robinson CG, Bradley JD. The treatment of early-stage disease. *Semin Radiat Oncol*. 2010 Jul;20(3):178-85. PMID: 20685580.
- McGarry RC, Song G, des Rosiers P, et al. Observation-only management of early stage, medically inoperable lung cancer: poor outcome. *Chest*. 2002 Apr;121(4):1155-8. PMID: 11948046.
- Raz DJ, Zell JA, Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. *Chest*. 2007 Jul;132(1):193-9. PMID: 17505036.
- Mohiuddin MM, Choi NC. The role of radiation therapy in non-small cell lung cancer. *Semin Respir Crit Care Med*. 2005 Jun;26(3):278-88. PMID: 16052429.
- Patel RR, Mehta M. Three-dimensional conformal radiotherapy for lung cancer: promises and pitfalls. *Curr Oncol Rep*. 2002 Jul;4(4):347-53. PMID: 12044245.
- Powell JW, Dexter E, Scalzetti EM, et al. Treatment advances for medically inoperable non-small-cell lung cancer: emphasis on prospective trials. *Lancet Oncol*. 2009 Sep;10(9):885-94. PMID: 19717090.
- Widesott L, Amichetti M, Schwarz M. Proton therapy in lung cancer: clinical outcomes and technical issues. A systematic review. *Radiother Oncol*. 2008 Feb;86(2):154-64. PMID: 18241945.
- Martel MK. Advanced radiation treatment planning and delivery approaches for treatment of lung cancer. *Hematol Oncol Clin North Am*. 2004 Feb;18(1):231-43. PMID: 15005291.
- Low DA, Moran JM, Dempsey JF, et al. Dosimetry tools and techniques for IMRT. *Med Phys*. 2011 Mar;38(3):1313-38. PMID: 21520843.
- Heinzerling JH, Kavanagh B, Timmerman RD. Stereotactic ablative radiation therapy for primary lung tumors. *Cancer J*. 2011 Jan-Feb;17(1):28-32. PMID: 21263264.
- Santos RS, Raftopoulos Y, Keenan RJ, et al. Bronchoscopic palliation of primary lung cancer: single or multimodality therapy? *Surg Endosc*. 2004 Jun;18(6):931-6. PMID: 15108108.
- Zhu JC, Yan TD, Morris DL. A systematic review of radiofrequency ablation for lung tumors. *Ann Surg Oncol*. 2008 Jun;15(6):1765-74. PMID: 18368456.
- Haasbeek CJ, Senan S, Smit EF, et al. Critical review of nonsurgical treatment options for stage I non-small cell lung cancer. *Oncologist*. 2008 Mar;13(3):309-19. PMID: 18378542.
- Das M, Abdelmaksoud MH, Loo BW Jr., et al. Alternatives to surgery for early stage non-small cell lung cancer-ready for prime time? *Curr Treat Options Oncol*. 2010 Jun;11(1-2):24-35. PMID: 20577833.
- Dagnault A, Ebacher A, Vigneault E, et al. Retrospective study of 81 patients treated with brachytherapy for endobronchial primary tumor or metastasis. *Brachytherapy*. 2010 Jul-Sep;9(3):243-7. PMID: 20122873.
- Ernst A, Feller-Kopman D, Becker HD, et al. Central airway obstruction. *Am J Respir Crit Care Med*. 2004 Jun 15;169(12):1278-97. PMID: 15187010.
- Amjadi K, Voduc N, Cruysberghs Y, et al. Impact of interventional bronchoscopy on quality of life in malignant airway obstruction. *Respiration*. 2008;76(4):421-8. PMID: 18758153.
- Morris CD, Budde JM, Godette KD, et al. Palliative management of malignant airway obstruction. *Ann Thorac Surg*. 2002 Dec;74(6):1928-32; discussion 32-3. PMID: 12643375.
- Cardona AF, Reveiz L, Ospina EG, et al. Palliative endobronchial brachytherapy for non-small cell lung cancer. *Cochrane Database Syst Rev*. 2008;(2):CD004284. PMID: 18425900.
- Yerushalmi R, Fenig E, Shitrit D, et al. Endobronchial stent for malignant airway obstructions. *Isr Med Assoc J*. 2006 Sep;8(9):615-7. PMID: 17058411.
- Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2011. Chapters available at www.effectivehealthcare.ahrq.gov.
- Pham B, Klassen TP, Lawson ML, et al. Language of publication restrictions in systematic reviews gave different results depending on whether the intervention was conventional or complementary. *J Clin Epidemiol*. 2005 Aug;58(8):769-76. PMID: 16086467.
- Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001 Apr;20(3 Suppl):21-35. PMID: 11306229.
- Carey TS, Boden SD. A critical guide to case series reports. *Spine (Phila Pa 1976)*. 2003 Aug 1;28(15):1631-4. PMID: 12897483.

33. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the effective health-care program. *J Clin Epidemiol*. 2010 May;63(5):513-23. PMID: 19595577.
34. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol*. 2011;64(4):407-15.
35. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009 Jul 21;6(7):e1000097. PMID: 19621072.
36. Mallick I, Sharma SC, Behera D, et al. Optimization of dose and fractionation of endobronchial brachytherapy with or without external radiation in the palliative management of non-small cell lung cancer: a prospective randomized study. *J Cancer Res Ther*. 2006 Jul-Sep;2(3):119-25. PMID: 17998689.
37. Langendijk H, de Jong J, Tjwa M, et al. External irradiation versus external irradiation plus endobronchial brachytherapy in inoperable non-small cell lung cancer: a prospective randomized study. *Radiother Oncol*. 2001 Mar;58(3):257-68. PMID: 11230886.
38. Stout R, Barber P, Burt P, et al. Clinical and quality of life outcomes in the first United Kingdom randomized trial of endobronchial brachytherapy (intraluminal radiotherapy) vs. external beam radiotherapy in the palliative treatment of inoperable non-small cell lung cancer. *Radiother Oncol*. 2000 Sep;56(3):323-7. PMID: 10974381.
39. Chella A, Ambrogio MC, Ribechini A, et al. Combined Nd-YAG laser/HDR brachytherapy versus Nd-YAG laser only in malignant central airway involvement: a prospective randomized study. *Lung Cancer*. 2000 Mar;27(3):169-75. PMID: 10699690.
40. Diaz-Jimenez JP, Martinez-Ballarín JE, Llunell A, et al. Efficacy and safety of photodynamic therapy versus Nd-YAG laser resection in NSCLC with airway obstruction. *Eur Respir J*. 1999 Oct;14(4):800-5. PMID: 10573224.
41. Boxem T, Muller M, Venmans B, et al. Nd-YAG laser vs bronchoscopic electrocautery for palliation of symptomatic airway obstruction: a cost-effectiveness study. *Chest*. 1999 Oct;116(4):1108-12. PMID: 10531180.
42. Kvale PA, Selecky PA, Prakash UB. Palliative care in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007 Sep;132(3 Suppl):368S-403S. PMID: 17873181.
43. Pan H, Rose BS, Simpson DR, et al. Clinical practice patterns of lung stereotactic body radiation therapy in the United States: a secondary analysis. *Am J Clin Oncol*. 2012 Apr 6; Epub ahead of print. PMID: 22495454.
44. Pan H, Simpson DR, Mell LK, et al. A survey of stereotactic body radiotherapy use in the United States. *Cancer*. 2011 Oct 1;117(19):4566-72. PMID: 21412761.
45. Dupuy DE. Image-guided thermal ablation of lung malignancies. *Radiology*. 2011 Sep;260(3):633-55. PMID: 21846760.
46. Goldberg SN, Hahn PF, Tanabe KK, et al. Percutaneous radiofrequency tissue ablation: does perfusion-mediated tissue cooling limit coagulation necrosis? *J Vasc Interv Radiol*. 1998 Jan-Feb;9(1 Pt 1):101-11. PMID: 9468403.
47. Gomez FM, Palussiere J, Santos E, et al. Radiofrequency thermocoagulation of lung tumours. Where we are, where we are headed. *Clin Transl Oncol*. 2009 Jan;11(1):28-34. PMID: 19155201.
48. Nguyen NP, Garland L, Welsh J, et al. Can stereotactic fractionated radiation therapy become the standard of care for early stage non-small cell lung carcinoma. *Cancer Treat Rev*. 2008 Dec;34(8):719-27. PMID: 18657910.
49. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol*. 2007 Jul;2(7 Suppl 3):S94-100. PMID: 17603311.
50. Moghissi K, Bond MG, Sambrook RJ, et al. Treatment of endotracheal or endobronchial obstruction by non-small cell lung cancer: lack of patients in an MRC randomized trial leaves key questions unanswered. Medical Research Council Lung Cancer Working Party. *Clin Oncol (R Coll Radiol)*. 1999;11(3):179-83. [Erratum in *Clin Oncol (R Coll Radiol)*; 1999;11(5):365.] PMID: 10465472.
51. Lee P, Kupeli E, Mehta AC. Therapeutic bronchoscopy in lung cancer. Laser therapy, electrocautery, brachytherapy, stents, and photodynamic therapy. *Clin Chest Med*. 2002 Mar;23(1):241-56. PMID: 11901914.

Full Report

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