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Number XX

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

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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

Structured Abstract

Objectives: To characterize the comparative effectiveness and harms of lung-directed therapies for non-small cell lung cancer (NSCLC) in three distinct patient populations: those with stage I NSCLC who have medical contraindications to definitive surgical resection; those with stage I NSCLC who are eligible for definitive surgical resection but decline surgery; and, those with inoperable NSCLC and symptoms (cough, dyspnea, hemoptysis) secondary to the presence of an endoluminal lesion and airway obstruction. For stage I NSCLC, the local interventions could include conformal radiotherapy modalities and radiofrequency ablation. For patients with airway obstruction due to an endoluminal NSCLC, local interventions could include those listed above for the stage I setting, plus conventional wide-field radiotherapy, brachytherapy, laser and mechanical debridement, luminal stents, cryoablation and photodynamic therapy.

Data Sources: MEDLINE®, EMBASE® and the Cochrane Controlled Trials Registry were searched from January 1995 to December 2011. A search of the grey literature included databases with regulatory information, clinical trial registries, abstracts and conference papers, and information from manufacturers.

Review Methods: We sought studies reporting overall survival, cancer-specific survival, local control, symptom relief, adverse events and quality of life among our populations of interest. Data were abstracted by Key Question (KQ) by a team of reviewers, with independent data verification. Study quality and the risk of bias of randomized trials were assessed using the convention of the United States Preventive Services Task Force (USPSTF). The quality and risk of bias of single-arm studies was assessed using the framework of Carey and Boden. The strength of the body of evidence was assessed according to the *AHRQ Methods Guide*.

Results: Four-thousand three-hundred records were identified through the literature search; 4,248 were excluded at various stages of screening, and 52 total records were included. Two studies presented data for both KQ1 and KQ2, but are not counted separately. Seven-hundred fifty-nine possible articles were identified in hand searches and from scientific information packets, but none were deemed relevant or unique. Thirty-three selected reports addressed KQ1, four (including two with both populations) addressed KQ2, and 17 addressed KQ3. No eligible comparative studies were identified for KQ1 or KQ2. Six randomized trials and 11 single-arm studies were identified for KQ3. All randomized, controlled trials were deemed to be of poor quality. Only one comparison was available per study, with no two studies examining the same set of interventions. Important outcomes of therapy for all KQs included overall survival, adverse effects, and quality of life.

Conclusions: Evidence for both KQ1 and KQ2 consists only of single-arm studies, with no direct comparisons. The evidence for KQ3 consists of randomized, controlled trials of one comparison only, precluding indirect comparisons. There is insufficient evidence to permit

conclusions on the comparative effectiveness of local therapies for inoperable or operable patients with stage I NSCLC or inoperable NSCLC patients with endoluminal tumor causing pulmonary symptoms.

Contents

Executive Summary ES-1
Introduction 1
Background 1
Non-Small Cell Lung Cancer (NSCLC) 1
Scope of the Review 6
Rationale 6
Key Questions 6
Organization of This Report 11
Methods 12
Topic Refinement and Review Protocol 12
Literature Search Strategy 12
Search Strategy 12
Grey Literature 13
Study Selection 13
Inclusion Criteria 13
Exclusion Criteria 14
Study Selection 14
Data Extraction & Management 15
Data Elements 15
Quality (Risk of Bias) Assessment of Individual Studies 16
Data Synthesis 18
Strength of the Body of Evidence 18
Applicability 18
Peer Review and Public Commentary 19
Results 20
Introduction 20
Overview 20
Results of Literature Searches 20
Electronic Search 20
Grey Literature (Publication Bias) 20
Key Question 1. Comparative Effectiveness of Local Interventions for Stage I NSCLC in Medically Inoperable Patients 22
Description of Included Studies 22
Key Points 22
Detailed Synthesis 26
Intervention-Associated Adverse Events 26
Key Question 2. Comparative Effectivness of Local Interventions for Stage I NSCLC in Medically Operable Patients 27

Key Points 29
Detailed Synthesis 29
Intervention-Associated Adverse Events 29
Risk of Bias For Individual Studies Addressing KQ1 and KQ2 30
Key Question 3. Comparative Effectiveness of Local Therapies for Symptoms Secondary to an Inoperable Obstructive Endoluminal NSCLC 31
Overview 31
Study Characteristics of Comparative Studies 31
Key Points 32
Description of Comparative Studies According To Intervention(s) 34
Study Characteristics of Noncomparative Studies 39
Discussion 42
Overview 42
Key Findings 42
Key Question 1: Local Interventions in Medically Inoperable Patients with Stage I Non-Small Cell Lung Cancer (NSCLC) 42
Key Question 2: Local Interventions in Medically Operable Patients with Stage I NSCLC 42
Key Question 3: Local Interventions for Inoperable Patients with NSCLC and Symptoms due to an Endoluminal Lesion 43
Strength of Evidence 43
Key Question 1 43
Key Question 2 44
Key Question 3 44
Relationship of the findings to existing information 46
Key Questions 1 and 2 46
Key Question 3 46
Applicability Of The Findings 47
Key Questions 1 and 2 47
Key Question 3 50
Implications for Clinical and Policy Decisionmaking 51
Limitations of the Comparative Effectiveness Review Process 51
Limitations of Evidence Base 51
Research Gaps 52
Overview 52
Key Questions 1 and 2 52
Key Question 3 54
Conclusion 55
List of Abbreviations 56
References 58

Tables

Table 1. TNM staging groups 2
Table 2. Summary of characteristics for studies that address Key Question 1 23
Table 3. Survival and local control outcomes for local interventions in medically inoperable patients with stage I NSCLC 26
Table 4. Studies reporting intervention-associated toxicities in stage I medically inoperable NSCLC patients 27
Table 5. Summary of characteristics for studies that address Key Question 2 28
Table 6. Survival and local control outcomes for local interventions in medically operable patients with stage I NSCLC 29
Table 7. Studies reporting intervention-associated toxicities in stage I medically operable NSCLC patients 30
Table 8. Carey and Boden quality rating summary 30
Table 9. Overview of Comparative Studies of Local Endobronchial Therapies 32
Table 10. Study characteristics of comparative studies 33
Table 11. Comparative effect of brachytherapy plus EBRT versus brachytherapy alone on obstructive symptoms in the Mallick study[64] 34
Table 12. Comparative effect of brachytherapy plus EBRT versus brachytherapy alone on quality of life outcomes in the Mallick study[64] 35
Table 13. USPSTF study quality ratings of the Mallick study[64] 35
Table 14. Comparative effect of brachytherapy plus EBRT versus EBRT alone on obstructive symptoms in the Langendjik study[65] 36
Table 15. USPSTF study quality ratings of the Langendjik study[65] 36
Table 16. Comparative effect of brachytherapy versus EBRT on obstructive symptoms in the Stout study[66] 37
Table 17. USPSTF study quality ratings of the Stout study[66] 37
Table 18. Comparative effect of laser plus brachytherapy versus laser alone on obstructive symptoms in the Chella study[67] 38
Table 19. USPSTF Study quality ratings of the Chella study[67] 38
Table 20. USPSTF Study quality ratings of the Jimenez study[68] 38
Table 21. USPSTF Study quality ratings of the Boxem study[69] 39
Table 22. Overview of noncomparative studies of local endobronchial therapies 39
Table 23. Treatment-related toxicities in noncomparative studies 41
Table 24. Strength of evidence for local interventions in medically inoperable stage I NSCLC patients 43
Table 25. Strength of evidence for local interventions in medically operable stage I NSCLC patients 44
Table 26. Strength of evidence for local therapies for symptoms secondary to an inoperable obstructive endoluminal NSCLC 45
Table 27. Summary of applicability of evidence for Key Questions 1 and 2 49
Table 28. Summary of applicability of evidence for Key Question 3 50

Figures

Figure 1. Analytical framework for comparative effectiveness of local nonsurgical definitive therapies for adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 or T2N0M0) medically inoperable NSCLC or those with documented stage I NSCLC who are deemed operable but elect nonsurgical intervention 7
Figure 2. Analytical framework for comparative effectiveness of local curative or palliative therapies for adult patients (age 18 years or older) with symptomatic inoperable endobronchial obstruction due to NSCLC. 8
Figure 3. Schematic for data management 15
Figure 4. PRISMA diagram for identified trials 21

Appendixes

Appendix A. Literature Search Strategy
Appendix B. List of Excluded Studies
Appendix C. Evidence Tables

Executive Summary

Background

Non-small cell lung cancer (NSCLC) refers to any type of epithelial lung cancer other than small cell lung cancer (SCLC).[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 squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, but several other types occur less frequently; all types can occur in unusual histological variants. Squamous cell carcinoma typically originates near a central bronchus. Adenocarcinoma and bronchioloalveolar carcinoma usually arise in peripheral lung tissue. Although frequently associated with cigarette smoke, adenocarcinomas may be found in patients who have never smoked.

Over 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 in 2010, an estimated 222,520 cases were expected to be diagnosed, with 157,300 deaths due to the disease.[2]

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 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 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 current Revised International System for Staging Lung Cancer, based on information from a clinical database of more than 5,000 patients, was subsequently adopted by the AJCC and UICC. [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, laboratory findings, or perceived risk of distant metastasis ultimately drives 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

Patients who are diagnosed with NSCLC 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 (includes distant metastases [M1] that were found at the time of diagnosis).

This Report aims to compare the effectiveness and harms of local therapies for the first two indications above. Comparisons of ablation versus surgery or systemic chemotherapy versus local therapy are outside the scope of this Report.

Local Nonsurgical Treatment Options for Stage I NSCLC

While surgery is the standard of care for patients with resectable stage I NSCLC, 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, 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 has been suggested 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 received no treatment because they were deemed medically inoperable; 53 percent of the latter succumbed 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]

Thoracic radiotherapy (RT) has a role in the definitive treatment of patients with stage I NSCLC who are deemed medically inoperable, or in those who decline surgery.[7, 9] Ideally, RT balances delivery of a cytotoxic dose of ionizing radiation to the tumor volume, while attempting to minimize adverse effects of radiation on adjacent normal lung tissue and thoracic structures. Several RT modalities have been used to treat patients with stage I NSCLC. Conventional wide-field 2DRT was used to treat medically inoperable patients with stage I NSCLC. However, it offered a relatively poor chance of cure with long-term survival rates of 3 percent to 13 percent overall, but perhaps 30 percent to 50 percent at 5 years in patients with T1 tumors.[6] This technique is no longer in routine use in modern radiation oncology practice in this setting. It is primarily of historical interest as a comparator for conformal RT techniques and thus was not considered in this CER.

Inadequate survival outcomes with 2DRT led to development and application of newer conformal RT 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 3-dimensional conformal radiation therapy (3DRT); intensity-modulated radiation therapy (IMRT); and stereotactic body radiation therapy (SBRT).[12-14] Charged particle-based therapy such as proton beam radiotherapy

(PBRT) is also available.[15] The optimal definitive external RT 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 of these RT procedures 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 secondary to 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 tumor 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 secondary to the small number of institutions that have experience with this technique and small reported patient numbers.[15, 20, 22]

Local Nonsurgical Treatment Options for Symptomatic Malignant Endobronchial NSCLC

Patients with airway obstruction from nonresectable primary or recurrent endoluminal lung tumors comprise 20-30 percent of NSCLC cases, manifested by 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. While these interventions typically represent palliative therapy, they may be performed in some patients with curative intent.

Patients with good performance status may benefit from external-beam RT (EBRT; conventional 2D-RT or conformal methods outlined above) to quickly ameliorate symptoms (e.g., 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.

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

The role of endobronchial BT for the palliative treatment of symptomatic patients with airway obstruction is unclear. It has been used as a palliative treatment in case of endobronchial tumor recurrence after EBRT. Endobronchial BT also may be an option for patients in whom EBRT fails to relieve symptoms, or those with endobronchial disease who require lung re-expansion before or in conjunction with radical RT.[26]

Several interventional methods involve tumor debulking to palliate symptoms in patients with advanced endobronchial NSCLC.[19, 25, 26, 28] Interventional bronchoscopy with mechanical debulking and stent placement can re-establish airway patency in patients with airway

obstruction due to a malignant endoluminal tumor. This procedure relieves dyspnea effectively and rapidly, although results may not always translate into improvements in overall quality of life.[25] Similarly, endobronchial stent placement can reduce respiratory distress in patients with malignant airway obstruction.[28] In a large cryosurgery series, 86 percent of 521 patients experienced improvement in one or more symptoms including cough, dyspnea, hemoptysis, and chest pain.[29] 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 this setting.

Objectives

This Agency for Healthcare Research and Quality-sponsored CER of local therapies for stage I (T1N0M0, T2N0M0) NSCLC and airway obstruction due to endoluminal NSCLC is intended as a comprehensive systematic review of the relative benefits and harms of lung-directed nonsurgical therapies in two disease settings encompassing three distinct patient populations (see PICOTS, following). Several local nonsurgical therapies are available for definitive treatment of inoperable stage I NSCLC, or those with operable lesions decline surgery. These 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, including external-beam RT 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, there is a substantial subset of stage I NSCLC patients 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 local 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 therapies in patients with inoperable NSCLC who have symptoms secondary to the presence of an endoluminal lesion. The optimal approach to these dire patients is not established. They often require urgent care, and typically have a short expected life-span at intervention, which may be palliative in most situations.

All the alternative modalities under consideration are clinically relevant and merit comparative evaluation due to uncertainty surrounding their optimal use in these settings. They are important to health care providers, patients, and policy makers given the substantial burden of disease posed by NSCLC, which typically affects older people who may have limited therapeutic choices, in a United States population that is growing increasingly elderly.

Key Questions

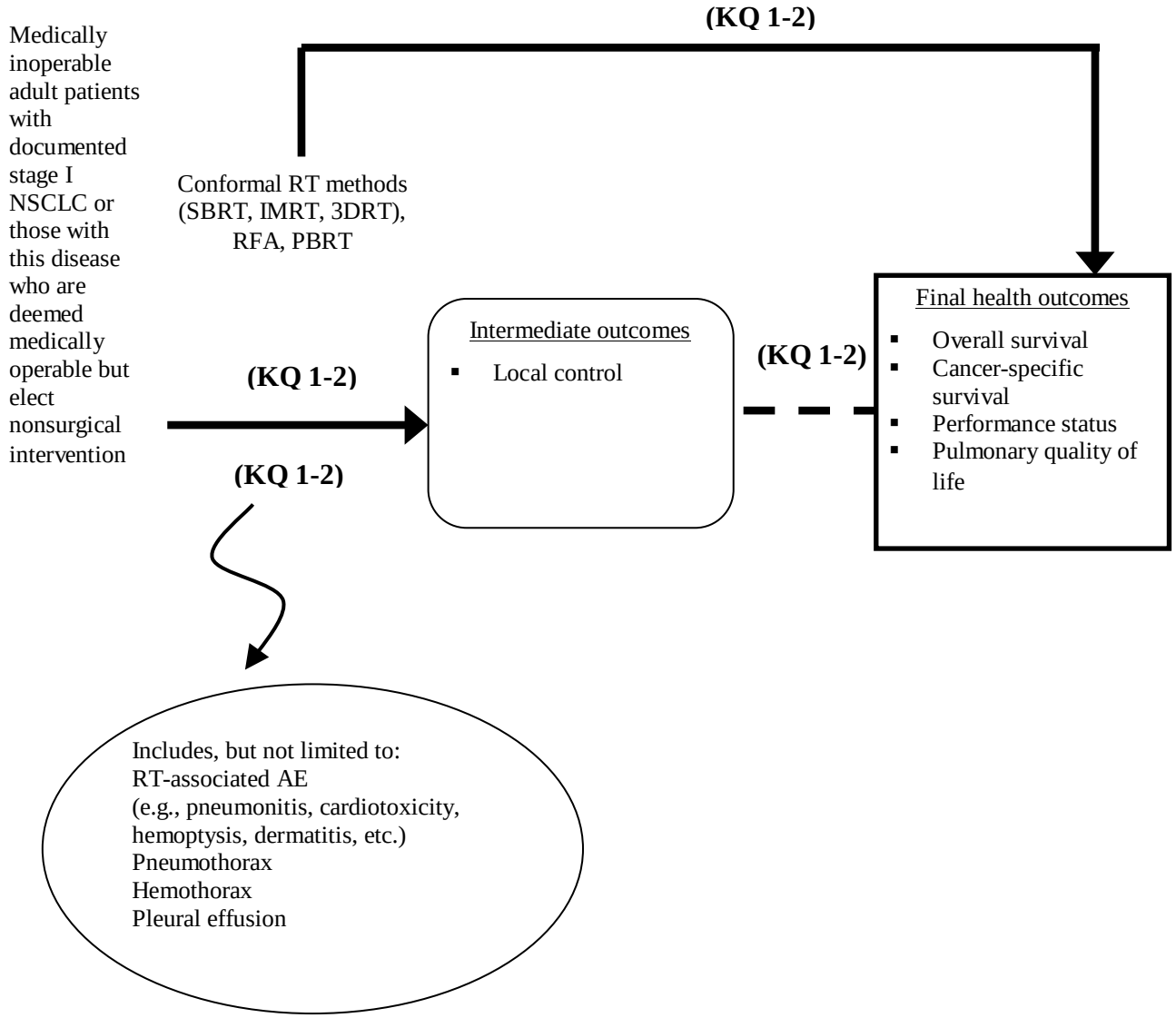
The Key Questions and CER analytical frameworks (Figures ES1 and ES2) are structured consistent with the PICOTS (Populations, Interventions, Comparators, Outcomes, Timeframes, Settings) framework, as laid out in the AHRQ EPC Methods Guide.[30]

Table ES1. PICOTS (Patient, Intervention, Comparator, Outcome, Timing, and Setting) for the Key Questions

PICOTS	KQ 1 and 2	KQ 3
Population	**1)Key Question 1:** Adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 and T2N0M0) non-small cell lung cancer 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 **2)Key Question 2:** Adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 and T2N0M0) non-small cell lung cancer who would otherwise be deemed surgical candidates according to current clinical criteria but decline surgery.	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 post obstructive pneumonitis, who were treated with curative or palliative intent.
Intervention	All interventions are first-line (definitive): • Conformal radiotherapy methods (including stereotactic body radiotherapy, three-dimensional conformal radiotherapy, intensity-modulated radiotherapy) • Proton beam therapy • Radiofrequency ablation	• Conventional 2D external beam radiotherapy • Conformal radiotherapy methods (including stereotactic body radiotherapy, three-dimensional conformal radiotherapy, intensity-modulated radiotherapy) • Brachytherapy • Radiofrequency ablation • Cryoablation • Laser therapy • Endobronchial debridement and stents • Photodynamic therapy • Electrocautery • Combinations were considered, for example endobronchial debridement plus a stent, compared with debridement alone; or, combination of 2D RT with brachytherapy compared with RT alone. • Because systemic therapy (chemotherapy) may be used with radiotherapy or local interventional methods in stage III or greater patients, we planned to collect that information to use in categorizing and assessing outcomes to ensure relevant and appropriate comparisons are made, particularly as they relate to possible harms. Such comparisons may be segregated and reported accordingly if it is not possible to discern interventional therapeutic effects.
Comparator	• Interventions were compared with each other as appropriate and noted above.	
Outcome	**Key Questions 1 and 2** • Final health outcomes: Overall survival, cancer-specific survival, performance status, pulmonary quality of life • Intermediate outcomes: Local control • Adverse outcomes: Includes, but not limited to, RT-associated AEs (e.g., pneumonitis, cardiotoxicity, hemoptysis, dermatitis, etc.), non-RT associated AEs (e.g., pneumothorax, hemothorax, pleural effusion)	• Final health outcomes: Overall survival, performance status, pulmonary quality of life • Intermediate outcomes: Local control, lung function, pulmonary symptoms (e.g., dyspnea, hemoptysis), respiratory tract infection • Adverse outcomes: Includes, but not limited to, RT-associated AEs (e.g., pneumonitis, cardiotoxicity, hemoptysis, dermatitis, etc.), non-RT associated AEs (e.g., pneumothorax, pleural effusion, transesophageal fistula, pericardial effusion)
Timing	**Key Questions 1 and 2** • The relevant periods occur at the time of treatment through followup over months (palliation) or years (overall survival).	• The relevant periods occur at the time of treatment through followup over months (palliation) or years (overall survival).
Setting	• Inpatient and outpatient	• Inpatient and outpatient

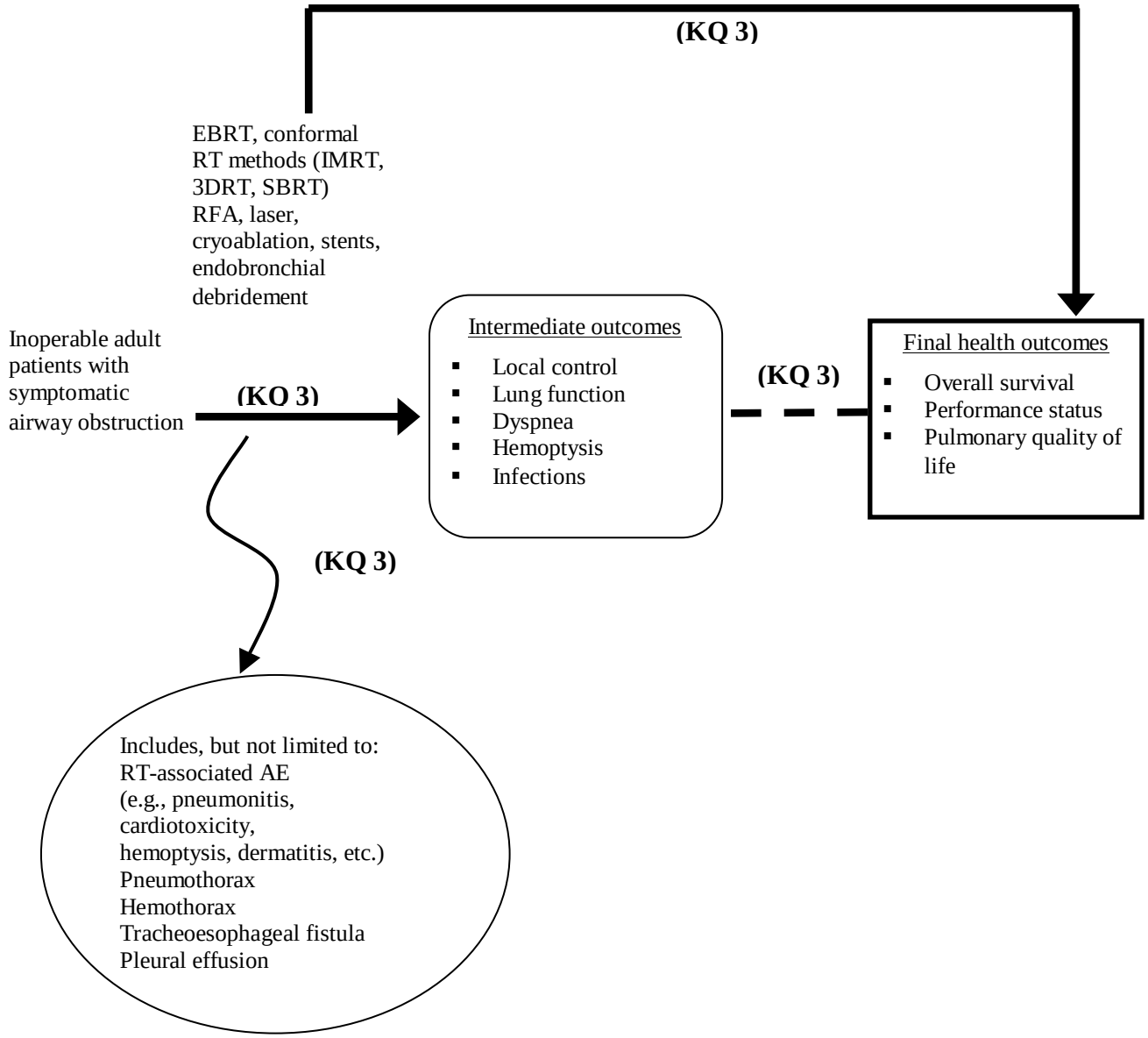
Analytic Framework

Figure ES1. 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 elect nonsurgical intervention



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; RT: radiotherapy; SBRT: stereotactic body radiotherapy

Figure ES2. Analytical framework for comparative effectiveness of local curative or palliative therapies for adult patients (age 18 years or older) with symptomatic inoperable airway obstruction due to NSCLC.



3DRT: three-dimensional radiotherapy; AE: adverse event; EBRT: external beam radiotherapy; FEV: forced expiratory volume; IMRT: intensity-modulated radiotherapy; KQ: key question; NSCLC: non-small cell lung cancer; PBRT: proton beam radiotherapy; RFA: radiofrequency ablation; RT: radiotherapy; SBRT: stereotactic body radiotherapy; YAG: yttrium aluminum garnet

Key Question 1.

- What are the comparative benefits and harms of local non-surgical 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 non-surgical 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 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 post obstructive pneumonitis?

Methods

Input from Stakeholders

The topic for this Report was received via the Effective Health Care Program website. Initially a panel of key informants gave input on draft Key Questions. These were posted on AHRQ's website for public comment on October 5, 2011 for 4 weeks and revised as necessary. The EPC drafted a protocol for the CER and recruited a panel of technical experts to provide high-level content and methodological expertise throughout the development of the review. The draft protocol was reviewed by the technical experts, and AHRQ personnel including the Task Order Officer for the project. The final protocol was posted to AHRQ's website on February 22, 2012.

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 December 31, 2011. 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, there is evidence to suggest that language restrictions do not change results of systematic review for conventional medical interventions.[31] Second, input from the Technical Expert Panel 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 can be found in Appendix A.

Grey literature was sought by searching for clinical trials (ClinicalTrials.gov), U.S. Food and Drug Administration website, and relevant conference abstracts (American Society of Clinical

Oncology, and American Society for Radiation Oncology). We limited the grey literature search until 2010. We reviewed Scientific Information Packets provided from the Scientific Resource Center. Study authors were not contacted for unpublished results. Our goal of gray literature search was to include only Phase III randomized trials that we had not identified in our electronic or hand searches.

Inclusion Criteria

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

Key Questions 1 and 2

1. Study included medically inoperable NSCLC stage I patients (T1N0M0 and T2N0M0) or medically operable NSCLC stage I patients (T1N0M0 and T2N0M0) who refuse surgery and
2. Such patients received only 1 of the following interventions as first-line (definitive) treatment
    - Conformal radiotherapy methods (including stereotactic body radiotherapy, three-dimensional conformal radiotherapy, intensity-modulated radiotherapy)
    - Proton beam therapy
    - Radiofrequency ablation
3. Study reported ≥ 1 of the following 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)
    - QOL
    - Adverse events

Key Question 3

1. Study included NSCLC patients of any stage with an endoluminal obstruction and
2. Such patients received ≥ 1 of the following interventions
    - Conformal radiotherapy methods (including stereotactic body radiotherapy, three-dimensional conformal radiotherapy, intensity-modulated radiotherapy)
    - Conventional 2D external beam radiotherapy
    - Proton beam therapy
    - Radiofrequency ablation
    - Brachytherapy
    - Cryoablation
    - Laser Therapy
    - Electrocautery
    - Endobronchial debridement and stents, and
3. Study reported data ≥ 1 of the following 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
    - QOL

- Adverse events

Exclusion Criteria

- Editorials, commentaries, abstracts, animal studies, case reports, non-English language, diagnostic accuracy studies
- Primary studies published prior to January 1, 1995 were excluded.
- For articles that included the same patients, interventions, and outcomes, we included the article that had the longest follow up, excluding the earlier paper(s). The latter were cross-indexed in the abstraction tables.
- For KQ 1 and 2, we planned to compare single interventions, for example two different conformal RT methods, or RFA compared with a conformal RT method. We excluded studies that mentioned the use of any post-intervention systemic (e.g., chemotherapy) or local therapy but did not define the therapy or disaggregate the clinical outcomes of recipients.

A list of excluded primary studies and reasons for exclusion are provided in Appendix B.

Data Abstraction and Quality Assessment

Electronic search results were transferred to EndNote® and subsequently into Distiller SR for study screening and selection. Using the study-selection criteria (outlined above in this section) for screening titles and abstracts, each citation was marked as: 1) eligible for review as full-text articles; 2) ineligible for full-text review. At least one training set (n=100) of representative titles and abstracts for each KQ was examined initially by all team members to assure uniform application of screening criteria. A subsequent set was assessed, establishing concordance among the team. Title and abstract screening was performed by two junior and one senior level team members. A study was excluded only when both team members made an independent decision to exclude it. In case of disagreement, the team lead adjudicated in consensus with all team members. A record of the reason for exclusion of each paper retrieved was kept in the Distiller SR database. While a paper may be excluded for multiple reasons, only one was recorded.

A test set of three papers relevant to the three KQs was evaluated in full-text by junior and senior team members, including the team leader, to ensure selection criteria were applied correctly. Subsequently, two junior team members and the team lead reviewed full-text articles independently to determine their inclusion in the systematic review. Team meetings were held regularly to discuss progress and to ensure 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 Distiller SR. A data abstraction guide was created that detailed the process of abstraction of data and definition of key data elements to ensure accuracy and consistency in data abstraction procedure across the team. 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 reviewer 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*,[30] the general approach to grading the risk of bias of individual comparative studies was performed by using a method used by the U.S. Preventive

Services Task Force.[32] The quality of the abstracted studies was assessed by one reviewer, and examined by the senior lead.

Our assessment of risk of bias in the included single-arm intervention studies was based on a set of study characteristics proposed by Carey and Boden.[33]

Data Synthesis and Analysis

Given the lack of appropriate comparative studies for all KQs, this evidence review did not incorporate formal data synthesis involving meta-analysis. The quality of individual studies was assessed as outlined above, and the strength of the body of evidence for each KQ was evaluated as follows.

Assessment of the Strength of Evidence

Selected studies were assessed for relevance against target populations, interventions and outcomes of interest. The system used for rating the strength of the overall body of evidence is outlined in the *Methods Guide* and is based on a system developed by the GRADE Working Group.[34] This system explicitly addresses the following domains: risk of bias, consistency, directness, and precision. Specific outcomes and comparisons were rated depending on the evidence found in the literature. The grade rating was made by independent reviewers, and disagreements were resolved by consensus adjudication.

The process of grading a body of evidence[34] was as follows. A body of evidence represented by randomized trial(s) would have a starting strength of high. A body of evidence represented by non-randomized comparative studies would generally have a starting strength of low. The strength of evidence would then by reduced by one level if there was high risk of bias, inconsistency or unknown consistency, indirectness and imprecision. If the study was fatally flawed, the strength of evidence was reduced by two levels.

The strength of evidence could be raised by at least one level for each of the following if:

- There was a large effect
- There was a dose response
- All plausible confounding and bias would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed.

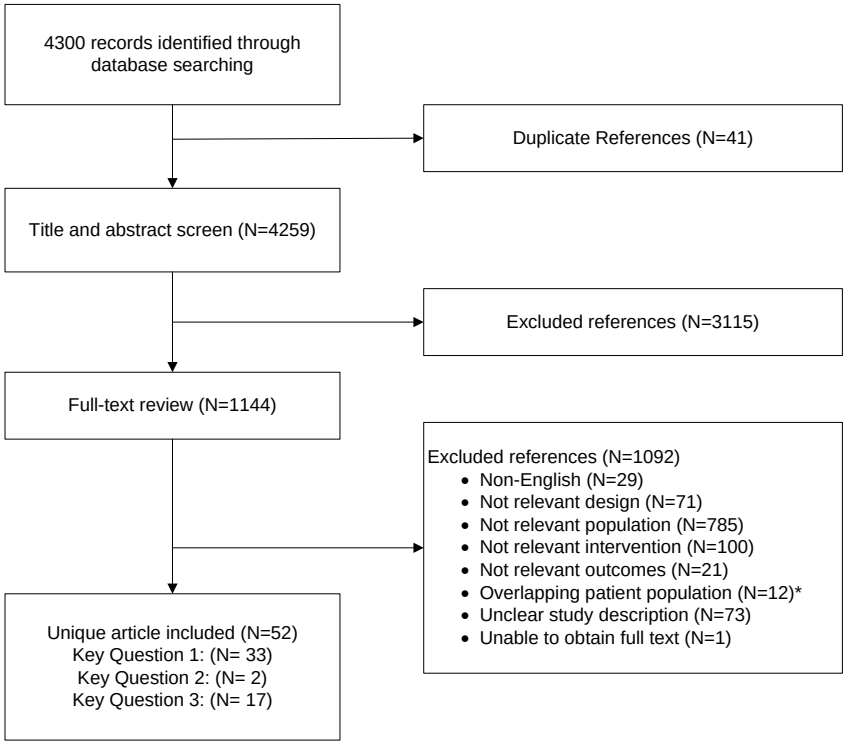
The overall strength of evidence was graded as “high” (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect); “moderate” (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate); “low” (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); or “insufficient” (indicating that evidence is either unavailable or does not permit estimation of an effect).

Results

Overview

A PRISMA diagram (Figure ES3) depicts the flow of search screening and study selection.

Figure ES3. PRISMA diagram for disposition of literature search results



*Overlapping patient population refers to the studies where same patients were included in more than one study. In all such cases, only one study was included to avoid over sampling. The decision to include the study was based upon nature of the study design (preference of RCT over observational study designs) and the clarity in reporting relevant patients and/or outcomes.

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

Key Points

- All evidence included in this Report for KQ1 is from single-arm studies. No evidence is available from any type of direct comparative study of one intervention versus another or versus a placebo or sham procedure.
- Evidence from 33 single-arm studies is insufficient to form conclusions about the comparative benefits or harms of SBRT (22 reports), 3DRT (seven reports), PBRT (three reports) and RFA (one report) in medically inoperable patients with stage I NSCLC.
- The results of interest for this Report comprise direct outcomes overall survival (OS) and cancer-specific survival (CSS); an indirect outcome, local control (LCT); and, radiation-associated toxicities, as shown in Figure ES1 above.
- Overall, post-treatment toxicities were not common across studies. No relative trend can be detected among interventions.
- It is unknown whether the limited evidence on adverse events reflects absence, or that the investigators did not systematically collect data or report them.

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

Key Points

- All evidence included in this Report for KQ2 is from single-arm studies. No evidence is available from any type of direct comparative study of one intervention versus another or versus a placebo or sham procedure
- Evidence from 4 single-arm studies is insufficient to form conclusions about the comparative benefits or harms of SBRT (3 reports) or PBRT (1 report) in medically operable patients with stage I NSCLC.
- The results of interest for this Report comprise direct outcomes OS and CSS; an indirect outcome, LC; and, radiation-associated toxicities as shown in Figure ES1.
- Post-treatment toxicities were not common across studies. No relative trend can be detected among interventions.
- It is unknown whether the limited evidence on adverse events reflects absence, or that the investigators did not systematically collect data or report them.

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

Key Points

- All RCTs included in this Report were poor quality according to the USPSTF rating criteria. Further analysis of this 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 versus brachytherapy alone; brachytherapy plus EBRT versus EBRT alone; brachytherapy versus EBRT; laser plus brachytherapy versus laser alone; laser versus electrocautery or photodynamic therapy) for local therapies in symptomatic inoperable patients with obstructive endoluminal NSCLC.
- The results of interest for this Report comprise direct outcomes (OS), symptom relief (cough, dyspnea, hemoptysis) and adverse events (radiation toxicities, other intervention-associated adverse events) as shown in Figure ES2.
- Overall, treatment-related toxicities varied according to type of intervention. Hemoptysis was the most common toxicity reported across studies. There may be under-reporting of treatment-related toxicities, as 3 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 strength of the body of evidence, we used the EPC approach developed for the Evidence-based Practice Center (EPC) program and referenced in the *Methods Guide* which is based on a system developed by the Grading of Recommendations Assessment, Development

and Evaluation (GRADE) Working Group[30, 35] This system explicitly addresses four required domains: risk of bias, consistency, directness, and precision, as outlined above in the Methods section.

Key Question 1

As shown in Table ES2, the overall strength of evidence 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.

Thirty-three single-arm studies were available. Direct outcomes of interest were OS, CSS, and toxicities. The risk of bias was high. The consistency of effect size direction cannot be determined 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.

Table ES2. Strength of evidence for local interventions in medically inoperable stage I NSCLC patients

Evidence Base	Risk of bias	Consistency	Directness	Precision	Overall Strength of Evidence
33 single-arm studies reported clinical outcomes associated with the use of 3DRT (7 studies,[50, 51, 54, 55, 75-77] total n = 240 patients), PBRT (3 studies,[36-38] total n = 144 patients), RFA (1 study,[39] n = 19 patients), and SBRT (22 studies,[40-61] total n = 1413 patients).	High	Unknown	Indirect comparisons Direct outcomes	Imprecise	Insufficient

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

Key Question 2

As shown in Table ES3, the overall strength of evidence is insufficient to form conclusions about the comparative benefical effects or toxicities of PBRT or SBRT in the treatment of stage I NSCLC in medically operable patients.

Four single-arm studies were available.[37, 56, 62, 63] Direct outcomes of interest were OS, CSS, and toxicities. The risk of bias was high. The consistency of effect size direction cannot be determined 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.

Table ES3. Strength of evidence for local interventions in medically operable stage I NSCLC patients

Treatment and Evidence Base	Risk of bias	Consistency	Directness	Precision	Overall Strength of Evidence
Four single-arm studies reported clinical outcomes associated with the use of SBRT (3 studies, [56, 62, 63] n = 278) or PBRT (1 study,[37] n = 28)	High	Unknown	Indirect comparisons Direct outcomes	Imprecise	Insufficient

n: number; NSCLC: non-small cell lung cancer; PBRT: proton beam radiotherapy; SBRT: stereotactic body radiotherapy

Key Question 3

Overall, evidence is insufficient to form conclusions about the benefits (symptom relief, survival) and harms (treatment related toxicities) of local therapies (brachytherapy plus EBRT versus brachytherapy alone; brachytherapy plus EBRT versus EBRT alone; brachytherapy versus EBRT; laser plus brachytherapy versus laser alone; laser versus electrocautery or photodynamic therapy) in symptomatic inoperable patients with obstructive endoluminal NSCLC.

Brachytherapy plus EBRT versus Brachytherapy Alone

The evidence for this comparison comprised one small RCT[64] (n=45, 15 patients per treatment arm). This study is considered to have a high risk of bias because the study 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 evidence for symptom relief, survival and treatment related toxicities is imprecise. Therefore, the SOE for brachytherapy plus EBRT versus brachytherapy alone was insufficient.

Brachytherapy plus EBRT versus EBRT alone

The evidence for this comparison comprised one small RCT[65] (n=95). This study was considered to have a high risk of bias primarily because the study was discontinued prematurely due to lack of patient accrual. This was considered a fatal flaw. The consistency of the evidence was unknown as it was a single RCT without confirmation from any other study. The evidence for symptom relief, survival and treatment related toxicities is imprecise. Therefore, the SOE for brachytherapy plus EBRT versus EBRT alone was insufficient.

Brachytherapy versus EBRT

The evidence for this comparison comprised one small RCT[66] (n=99). This study is considered to have a high risk of bias because the study failed to adjust for potential confounding secondary to cross-over of a large proportion of patients between treatment arms during the study period. This was considered a fatal flaw. The consistency of the evidence was unknown as it was a single RCT without confirmation from any other study. The evidence for symptom relief and treatment related toxicities is imprecise. The evidence for survival was precise. Therefore, the SOE for brachytherapy versus EBRT alone was insufficient.

Laser plus Brachytherapy versus Laser Alone

The evidence for this comparison comprised one small RCT[67] (n=29). This study is 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 evidence for symptom relief, survival and treatment related toxicities is imprecise. Therefore, the SOE for laser plus brachytherapy versus laser alone was insufficient.

Laser versus Photodynamic Therapy

The evidence for this comparison comprised one small RCT[68] (n=31). This study was considered to have a high risk of bias primarily because the treatment arms had serious imbalances at the baseline. The proportion of patients with stage III-IV cancer was much smaller in the photodynamic group (57%, 8 of 14) than the laser group (88%, 15 of 17). This was considered a fatal flaw. The consistency of the evidence was unknown as it was a single RCT

without confirmation from any other study. The evidence for treatment related toxicities is imprecise. The evidence for survival was precise. Therefore, the SOE for brachytherapy versus EBRT alone was insufficient.

Laser versus Electrocautery

The evidence for this comparison comprised one small non-randomized comparative study[69] (n=29). This study is considered to have a high 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 percent) as compared with the electrocautery group (53 percent). Further, the mean time from diagnosis to study treatment was different in the two groups (4.7 versus 7.5 months in laser versus electrocautery group). The consistency of the evidence was unknown as it was a single RCT without confirmation from any other study. The evidence for symptom relief and survival is imprecise. Therefore, the SOE for laser versus electrocautery was insufficient.

Table ES4. Strength of evidence for local therapies for symptoms secondary to an inoperable obstructive endoluminal NSCLC

Treatment and evidence base	Outcome	Unit of Measure	Risk of bias	Consistency	Directness	Precision	SOE
Brachytherapy plus EBRT versus brachytherapy alone (1 RCT, n=45)[64]	Symptom relief	Incidence and response rate	High	Unknown	Yes	Imprecise	Insufficient
	QOL	EORTC QLQ-C30 & LC 13 V3.0					
	Treatment toxicity	Incidence of Grade ≥II RTOG morbidity scoring scriteria					
Brachytherapy plus EBRT versus EBRT alone (1 RCT, n=95)[65]	Symptom relief	Response rate	High	Unknown	Yes	Imprecise	Insufficient
	Survival	Overall survival					
	Treatment toxicity	Incidence					
Brachytherapy versus EBRT (1 RCT, n=99)[66]	Symptom relief	% improvement	High	Unknown	Yes	Imprecise	Insufficient
	Survival	Overall survival	High	Unknown	Yes	Precise	Insufficient
	Treatment toxicity	Incidence	High	Unknown	Yes	Imprecise	Insufficient
Nd-YAG plus Brachytherapy versus Nd-YAG alone (1 RCT, n=29)[67]	Symptom relief	Speiser's index	High	Unknown	Yes	Imprecise	Insufficient
	Survival	Overall survival					
	Treatment toxicity	Incidence					
Photodynamic Therapy versus Laser (1 RCT, n= 31)[68]	Survival	Overall survival	High	Unknown	Yes	Precise	Insufficient
	Treatment toxicity	Incidence	High	Unknown	Yes	Imprecise	Insufficient
Nd-YAG versus Electrocautery (1 NRC, n=29)[69]	Survival	Mean survival	High	Unknown	Yes	Imprecise	Insufficient
	Symptom relief	% response					

BCHY: brachytherapy; EBRT: external beam radiotherapy; EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; KQ: key question; n: number; N: total sample size of the study; Nd-YAG: neodymium-doped yttrium aluminum garnet; NSCLC: non-small cell lung cancer; NRC: nonrandomized comparative study; QOL: quality of life; RCT: randomized controlled trial; RTOG: Radiation Therapy Oncology Group; SOE: strength of evidence

Applicability of the Findings

Comments will be limited to relevance of the PICOTS (population, intervention, comparator, outcomes, timing, and setting) elements rather than applicability.[70] The PICOTS format provides a practical and useful structure to this exercise and is employed in the subsections below.[70]
Our results show there is no direct comparative evidence to support a decision among 3DRT, PBRT, RFA or SBRT in stage I NSCLC patients. There is a paucity of comparative evidence among any of the interventions considered in KQ3. 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. The last issue is outside the scope of this CER.

Key Question 1 and 2

Table ES5. Summary of applicability of evidence for Key Question 1 and Key Question 2

Domain	Applicability of Evidence
Populations	• Overall the patients included in the single-arm studies were not suitable for surgery, or were suitable for surgery but declined it. • The patients with stage I NSCLC in the studies included in this report appear representative of cases that would be considered for a local intervention. • Patients typically were in their late 60s to mid-70s, congruent with the incidence of stage I NSCLC that 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 than the inoperable population of KQ1. Compared with the latter, however, they represent a somewhat healthier group, albeit perhaps not compared with the population that undergoes surgery.
Interventions	• 3DRT, IMRT and SBRT represent a progression of technological advances in the delivery of conformal photon radiotherapy. The major benefit of each relative to traditional wide-field 2DRT is the ability to deliver tightly focused cytotoxic radiation to a tumor volume that is precisely delineated using a CT-based planning system. • 3DRT represents a minimum technical capability for delivery of conformal radiotherapy, and is widely available. • IMRT is not as widely available as 3DRT, and requires a higher level of planning and quality assurance. • The institutional programmatic requirements for SBRT are similar to those of IMRT. • SBRT is not as widely available as 3DRT or IMRT, but our literature review suggests there has been growing interest in this technology in this setting, to the point that is may supplant the older technologies in the KQ1 and KQ2 settings. • This CER did not allow for a rigorous and systematic comparison of the relative performance of local therapies stratified by technological factors. How these factors may alter health outcomes remains unclear. • The applicability of the evidence for PBRT and RFA is unknown due to limited evidence.
Comparators	See above for Intervention
Outcomes	• The major health outcomes in this CER are OS, CSS, and LCT, typically reported over a period of one to five years. • OS is the gold standard direct outcome for any cancer intervention study. • CSS reflects the true effect of a cancer intervention on the disease. It 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 still 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 around systemic chemotherapy. This is a potentially perilous position for the medically frail patients considered in KQ1, and perhaps many of those in KQ2.
Setting	• The evidence for KQ 1 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 on-going 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; n: number; LCT: local control; NSCLC: non-small cell lung cancer; OS: overall survival; PBRT: proton beam radiotherapy; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy

Key Question 3

Table ES6. Summary of applicability of evidence for Key Question 3

Domain	Applicability of Evidence
Populations	• The patients in the studies included in this report appear 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 61-68 years and this is congruent with the incidence of NSCLC that tends to rise with age.
Interventions	• The 5 single modality interventions (brachytherapy, EBRT, electrocautery, laser, photodynamic) and 2 dual modality interventions (laser plus brachytherapy and brachytherapy plus EBRT) represent a general landscape of current treatments options for patients with endoluminal obstructive NSCLC and therefore are applicable.
Comparators	• See above for Intervention
Outcomes	• The major outcomes of interest were symptom relief, overall survival, disease specific survival, quality of life and treatment-related toxicity. • Though OS is the gold standard direct outcome for any cancer intervention study, it may not be the best measure of efficacy of a palliative intervention in symptomatic patients. • Immediate relief of obstructive symptom and improvement in quality of life 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 Outcomes Measures),[71] both generic and disease specific instruments exists 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 EORTC QLQ-C30, EORTC QLQ-LC13 and FACT-L. However, QOL data was reported only by one small study of the six comparative studies. Therefore, applicability of the current evidence base on QOL cannot be determined.
Setting	• 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 as part of our systematic review.

EBRT: external beam radiotherapy; EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D: self-report questionnaire; NSCLC: non-small cell lung cancer; QOL: quality of life; SF-36: Short Form 36 Health Survey

There were multiple shortcomings with the current evidence base for KQ3 that precludes interpretation about general applicability. Firstly, the comparative benefits and harms of various endobronchial treatments are still unknown because of lack of good quality randomized controlled trials. The available studies were all poor quality, often small and not powered to detect a pre-specified clinically meaningful difference in a standardized outcome of interest. Secondly, 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. Thirdly, there was a wide variation in the outcomes measures to report symptom relief in the current studies. Fourthly, many studies did not report the frequency, the process or the 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.

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 to our findings for KQ 1 and 2, and two publications relevant to KQ3.[27, 72] Our Report offers the first comprehensive systematic review on this topic.

Limitations of Current Review and Evidence Base

The primary limitation is the lack of comparative trials of any design for KQ1 and 2, and a paucity of comparative evidence for KQ3. Even though comparative studies (5 RCTs and 1 nonrandomized comparative study) were available for KQ3, significant limitations in the quality and quantity of evidence base led us to conclude that the evidence was insufficient to make conclusions about comparative effectiveness of local interventions to treat endobronchial obstructions in NSCLC patients.

Research Gaps Key Questions 1 and 2

Two international randomized, Phase III clinical trials of surgical resection versus SBRT are recruiting patients (NCT01336894 and NCT 00840749). We identified no ongoing randomized trials that would compare among the interventions or settings addressed in KQ1 or 2.

The absence of comparative evidence acquired through standardized protocols is the most important research gap we have identified. The two RCTs mentioned above will not reveal relative outcomes among local interventions. There is a need for randomized trials to be performed in the United States population. Assuming a number of impediments (see below) can be surmounted, we see a need for rigorous study as follows:

- RCTs of local interventions (e.g., SBRT, 3DRT, IMRT, RFA) in medically inoperable stage I patients, incorporating the following:
    - Standardized patient selection criteria involving thoracic surgeon, medical oncologist, and radiation oncology consultation to assure comparability of patients and minimize bias. Key factors 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. For radiotherapy, key interventional factors include the radiotherapy 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, PBRT). RFA factors include power source, power delivered, intralesional temperature achieved, time course of therapy, the type of probe(s) used, and their placement within the lesion.
    - Prespecified followup criteria and methods, in particular notation of subsequent systemic therapy. The latter is a key concern because it is not possible to determine the effect of an intervention administered with systemic therapy.
    - Rigorous, standardized reporting that accounts for all patients and treatments received. Analysis of studies that enroll operable and inoperable patients is possible only if the findings are reported disaggregated. Rigorous methods for conduct of RCTs is urged, particularly intent-to-treat analysis and adjustment of survival data for patients who develop recurrent disease go on to receive systemic therapy. Primary outcomes include overall survival, cancer-specific survival, and

local control. Prespecified, systematic collection of adverse events using the latest validated criteria (e.g., NCI CTCAE criteria) is necessary to permit accurate assessment of relative benefits and risks of the interventions.

- Extrapolating results of randomized comparative trial results among inoperable patients that identify the most effective and safe local intervention(s) into medically operable patients who decline surgery, incorporating the following, with key factors, methods, and outcomes listed in the preceding bullet points:
    - Standardized patient selection criteria involving thoracic surgeon, medical oncologist, and radiation oncology consultation to assure comparability of patients and minimize bias.
    - Standardized intervention protocols with training and quality assurance programs within and across participating institutions.
    - Prespecified followup criteria and methods, in particular notation of subsequent systemic therapy.
    - Rigorous, standardized reporting that accounts for all patients and treatments received.

However, a number of general impediments to conducting adequate trials may exist:

- Even though there are no direct comparative trials among the local interventions to suggest one is more effective than another, survey data suggest SBRT is quickly becoming a widely-used modality for stage I NSCLC patients who are medically inoperable or choose to forgo surgical resection.[73, 74]
- In comparison to 3DRT or IMRT, SBRT necessitates fewer treatments, a significant factor that may drive decisions among patients and clinicians.
- Ready access to a specific intervention may be a decision point in clinical practice, in particular considering whether they are available at community-based hospitals or tertiary centers, which could drive patients and their referring physicians toward a specific technology. Nearly 40 percent of solo practitioners in a survey study reported treating patients with SBRT, which suggests this technology is becoming accessible within the broader radiation oncology community.[73, 74]

Key Question 3

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 randomized controlled trials 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 randomized controlled trials 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 toxicities data from various bronchoscopic interventions used for treating endoluminal obstructions from actual clinical practice setting.

While reviewing the published literature we came across two studies that planned a RCT to compare local endobronchial interventions in patients with endobronchial NSCLC but were unable to complete the trial due to lack of patient accrual or never published the trial results. Among these 2 studies, study by Moghissi et al.,[75] is most notable. The objective of this RCT was to compare 2 treatment policies in terms of: symptom relief, respiratory function, performance status, quality of life and survival. This study planned to recruit 400 patients in 3 years at 24 clinical centers in the UK. 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. Another study by Langendijk[65] that aimed to randomize patients to brachytherapy plus EBRT or EBRT alone arm discontinued their study due to lack of patient accrual before they could complete the planned enrollment of 160 patients.

NSCLC patients with endoluminal obstructions are particularly difficult to randomize in trials because of many issues particularly ethical issues in randomizing critically ill patients. Most of these bronchoscopic interventions are considered complementary and are used sequentially in a clinical setting[76] and therefore randomizing 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 barriers are likely to obviate successful conduct if more RCTs are undertaken in the future.

Thus we propose a prospective cohort study may be able to answer the questions about relative harms and benefits of local endobronchial interventions. Though concerns of selection bias and unknown confounders will always exist in this study design, addressing and collecting data about most relevant confounders a priori can provide much needed informative answers about comparative benefits and harms of these therapies in population of interest. We recommend that the research team for conducting such a study should be multi-disciplinary including oncologists experienced in treating NSCLC patients with endobronchial obstruction, methodologist with expertise in quality of life measurement, clinical researchers with expertise in planning and conduct of large cohort multicentric studies and ethicists. Relevant outcomes that should be measured in such a study should include symptom control, quality of life, survival and treatment-related adverse effects. Data related to symptom control should be captured using a standardized validated tool applied uniformly across all interventions. Generic instruments such as SF-36 and EQ-5D should be used in conjunction with lung cancer specific measures such as EORTC QLQ-C30, EORTC QLQ-LC13 and FACT-L to measure QOL data.

Treatment-related adverse events should be assessed from the date of the procedure extending to a reasonable period of time preferably until death using standardized and well-defined criteria with an independent causality analysis. All such adverse events should be assessed not just by clinicians but the study design should incorporate a process to capture and report adverse event that occur when patients are under direct medical supervision such as home or long term care facility. Data on all potential prognostic covariates should include but not 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 data on the operator (expertise, years of experience, size of the facility).

Conclusions

There is insufficient evidence to permit conclusions on the comparative effectiveness of local 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, adverse effects, and quality of life.

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Introduction

Background

Non-Small Cell Lung Cancer (NSCLC)

NSCLC refers to any type of epithelial lung cancer other than small cell lung cancer (SCLC).[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 squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, but several other types occur less frequently; all types can occur in unusual histological variants. Squamous cell carcinoma typically originates near a central bronchus. Adenocarcinoma and bronchioloalveolar carcinoma usually arise in peripheral lung tissue. Although frequently associated with cigarette smoke, adenocarcinomas may be found in patients who have never smoked.

Over 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 in 2010, an estimated 222,520 cases were expected to be diagnosed, with 157,300 deaths due to the disease.[2]

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 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 involving the esophagus causing dysphagia, compression of laryngeal nerves causing hoarseness, or compression of 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.

NSCLC Staging

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 current Revised International System for Staging Lung Cancer, based on information from a clinical database of more than 5,000 patients, was subsequently adopted by the AJCC and UICC.[4] Current TNM staging groups are summarized in Table 1.

Table 1. TNM staging groups

Overall stage	T	N	M
Stage 0	Tis (in situ)	N0	M0
Stage IA	T1a, b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a, b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1, T2	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M 1a, b

M: presence of absence of distant metastases; N: extent of regional lymph node involvement; T: size of the primary tumor

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, laboratory findings, or perceived risk of distant metastasis ultimately drives 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

Patients who are diagnosed with NSCLC 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, which are not typically used in this setting until or unless a patient develops recurrence or distal disease

- 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
- Inoperable distant metastatic disease (includes distant metastases [M1] that were found at the time of diagnosis).

Surgical Resection for Stage I NSCLC

Based on the International Association for the Study of Lung Cancer (IASLC) database of more than 100,000 patients treated between 1990 and 2002, about 20-25 percent of NSCLC patients present with stage I (T1N0M0, T2N0M0) disease.[77] Resection is considered the standard of care for surgically eligible patients in this setting. This would preferably be a lobectomy for most patients, alternatively a pneumonectomy for tumors in which sleeve resection or bronchoplasty would not allow achievement of adequate margins.[9] Data from the IASLC database of patients shows 5-year overall survival rates may range from 71-77 percent for stage IA NSCLC and 35-58 percent for stage IB disease.[78] Improvements in the use of staging methods including FDG-PET and CT have led to improved surgical outcomes, exemplified by a report

including 405 stage IA and Stage IB patients who had a 5-year overall survival (OS) of 80 percent and 72 percent, respectively.[79]

Surgical morbidity and mortality are typically low in most modern series, with major complications reported in about 6 percent of lobectomy cases and 18 percent of pneumonectomy cases in a large study.[80] A recent systematic review reported postsurgical 30-day mortality ranged from 7 percent to 25 percent among patients with poor ventilatory function, with a weighted mean of 10 percent.[50]

Local Nonsurgical Treatment Options For Stage I NSCLC

While surgery is the standard of care for patients with resectable stage I NSCLC, 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, 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 has been suggested 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 received no treatment because they were deemed medically inoperable; 53 percent of the latter succumbed 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]

Radiotherapy

Thoracic radiotherapy (RT) has a role in the definitive treatment of patients with stage I NSCLC who are deemed medically inoperable, or in those who decline surgery.[7, 9] Ideally, RT balances delivery of a cytotoxic dose of ionizing radiation to the tumor volume, while attempting to minimize adverse effects of radiation on adjacent normal lung tissue and thoracic structures. Several RT modalities have been used to treat patients with stage I NSCLC, as follows.

Conventional Two-Dimensional External-Beam Radiotherapy (2DRT)

Conventional 2DRT was until recently used to treat medically inoperable patients with stage I NSCLC. It offered a relatively poor chance of cure with long-term survival rates of 3 percent to 13 percent overall, but perhaps 30 percent to 50 percent at 5 years in patients with T1 tumors.[6] This technique is no longer in routine use in modern radiation oncology practice in this setting. It is primarily of historical interest as a comparator for conformal RT techniques and thus was not considered for the stage I setting in this comparative effectiveness review (CER).

External-Beam Conformal Radiotherapy (EBRT) Options

Inadequate survival outcomes with 2DRT led to development and application of newer conformal RT 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 3-dimensional conformal radiation therapy (3DRT); intensity-modulated radiation therapy (IMRT); and stereotactic body radiation therapy (SBRT).[12-14] Charged particle-based therapy such as proton beam radiotherapy (PBRT) is also available.[15]

3-Dimensional Conformal Radiation Therapy (3DRT)

3DRT employs computed tomography (CT) simulation, allowing for more accurate dose calculations by taking into account axial anatomy and complex tissue contours. Three-dimensional anatomic information from diagnostic CT scans are used to deliver multiple (100-200) highly focused beams of radiation that converge at the tumor site.[6] This allows accurate and precise conformity of the radiation to the tumor volume, with very rapid dose fall-off in surrounding normal lung parenchyma.

Intensity-Modulated Radiation Therapy (IMRT)

IMRT allows for the modulation of both the number of fields and the intensity of radiation within each field, allowing for greater control of the dose distribution to the target.[17, 20, 21] A potential theoretical benefit of IMRT is the ability to deliver higher doses to the tumor than with other methods, with greater tumoricidal effectiveness. Dose-volume histogram studies suggest IMRT allows better conformality of the high-dose volume to the tumor. However, questions continue about the relative benefits and harms of this technique because IMRT increases the volume of lung that receives a low radiation dose, and may actually increase the rate of injury.[13]

Stereotactic Body Radiation Therapy (SBRT)

SBRT delivers very high, conformal ablative doses of radiation in fewer treatment sessions (generally 3-8 fractions), with the potential to cause less damage to surrounding normal tissue.[18] SBRT regimens generally deliver doses greater than 10 grays (Gy) per fraction, with continuous monitoring of tumor motion during the breathing cycle via four-dimensional CT imaging. A theoretical advantage of SBRT relative to other modalities is its ability to deliver very high biologically effective doses above 100 Gray equivalent (GyE) that are needed to ablate the tumor and sterilize the tumor margins while minimizing damage to adjacent normal tissue.

Proton Beam Radiotherapy (PBRT)

PBRT delivers high doses of radiation to the tumor. Proton beams enter the body with a low radiation dose, stop at the tumor, match its shape and volume or depth, and deposit the bulk of their cytotoxic energy within the tumor; thus this type of treatment may cause less damage to surrounding healthy tissue.[15]

Summary: Radiotherapy

The optimal definitive external RT 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 of these RT procedures 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 secondary to the small number of institutions that have experience with this technique and small reported patient numbers.[15]

Interventional Treatment Options

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 tumor 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 secondary to the small number of institutions that have experience with this technique and limited patient data.[15, 20, 22]

Brachytherapy was used for definitive treatment of stage I nonsurgical patients, but is now considered appropriate only as an adjunct to surgery.[81] It was not considered in the stage I setting in this CER.

Local Nonsurgical Treatment Options for Symptomatic Malignant Endobronchial NSCLC

Patients with airway obstruction from non-resectable primary or recurrent NSCLC comprise 20-30 percent of NSCLC cases, manifested by 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 to stop bleeding. While these interventions typically represent palliative therapy, they may be performed in some patients with curative intent.

Radiotherapy

Patients with good performance status may benefit from external-beam RT (conventional 2D-RT or conformal methods outlined above) to quickly ameliorate symptoms (e.g., 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 close to radiosensitive organs or other anatomic structures, interventional options may become necessary.

Interventional Options

Brachytherapy

Endobronchial brachytherapy (BT) is another option for treating airway obstruction and can be used alone, or in combination with external beam radiotherapy (EBRT) to boost the total dose of irradiation used.[26, 27] It has been used in combination with high-dose EBRT as a potential curative primary treatment in selected cases. Serious complications have been described with endobronchial BT, including massive hemoptysis, tracheoesophageal fistulas, bronchial stenosis and radiation bronchitis.[27]

The role of endobronchial BT for the palliative treatment of symptomatic patients with airway obstruction is unclear. It has been used as a palliative treatment in case of endobronchial tumor recurrence after EBRT. Endobronchial BT also may be an option for patients in whom EBRT fails to relieve symptoms, or those with endobronchial disease who require lung re-expansion before or in conjunction with RT.[26]

Bronchoscopy and Stents, Cryoablation and Photodynamic Therapy

Several interventional methods involve tumor debulking to palliate symptoms in patients with advanced endobronchial NSCLC.[19, 25, 26, 28] Interventional bronchoscopy with mechanical debulking and stent placement can re-establish airway patency in patients with malignant airway obstruction due to locally advanced disease. This procedure relieves dyspnea effectively and rapidly, although results may not always translate into improvements in overall quality of life.[25]

Similarly, endobronchial stent placement can reduce respiratory distress in patients with malignant airway obstruction.[28] In a large cryosurgery series, 86 percent of 521 patients experienced improvement in one or more symptoms including cough, dyspnea, hemoptysis, and chest pain.[29] Laser resection involving the neodymium-doped yttrium aluminum garnet (Nd-YAG) laser and photodynamic therapy (PHDT) using porfimer sodium have been investigated in this setting with suggestion of symptomatic improvement in some cases.[19] Radiofrequency ablation also has been used in this setting.

Scope of the Review

This Agency for Healthcare Research and Quality (AHRQ) -sponsored CER of local therapies for stage I (T1N0M0, T2N0M0) NSCLC and airway obstruction due to NSCLC is intended as a comprehensive systematic review of the relative benefits and harms of lung-directed nonsurgical therapies in two disease settings encompassing four distinct patient populations (see PICOTS, below). Several local nonsurgical therapies are available for definitive treatment of inoperable stage I NSCLC, or those with operable lesions who decline surgery. These 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, including external-beam RT methods, brachytherapy, surgical debridement and stent placement, and others (e.g., Nd-YAG laser, RFA, cryoablation).

Rationale

Surgery is currently regarded as the standard of care for eligible patients with stage I NSCLC. However, alternative treatments are needed for a subset of stage I NSCLC patients for whom surgery is contraindicated because 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 the CER. Instead the CER is focused on local modalities for inoperable patients in Key Question 1, and in operable patients in Key Question 2.

Key Question 3 addresses the comparative benefits and harms of local therapies in patients with inoperable NSCLC who have symptoms secondary to the presence of an endoluminal lesion. The optimal approach to these dire patients is not established, they often require urgent care, and typically have a short expected life-span at intervention, which may be palliative in most situations.

All the alternative modalities under consideration are clinically relevant and merit comparative evaluation due to uncertainty surrounding their optimal use in these settings. They are important to health care providers, patients, and policy makers given the substantial burden of disease posed by NSCLC, which typically affects older people who may have limited therapeutic choices, in a United States population that is growing increasingly elderly.

Key Questions

The Key Questions and CER analytical frameworks (Figure 1 and Figure 2) are structured consistent with the PICOTS (Populations, Interventions, Comparators, Outcomes, Timeframes, Settings) framework, as laid out in the AHRQ EPC Methods Guide.[30]

Figure 1. Analytical framework for comparative effectiveness of local nonsurgical definitive therapies for adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 or T2N0M0) medically inoperable NSCLC or those with documented stage I NSCLC who are deemed operable but elect nonsurgical intervention

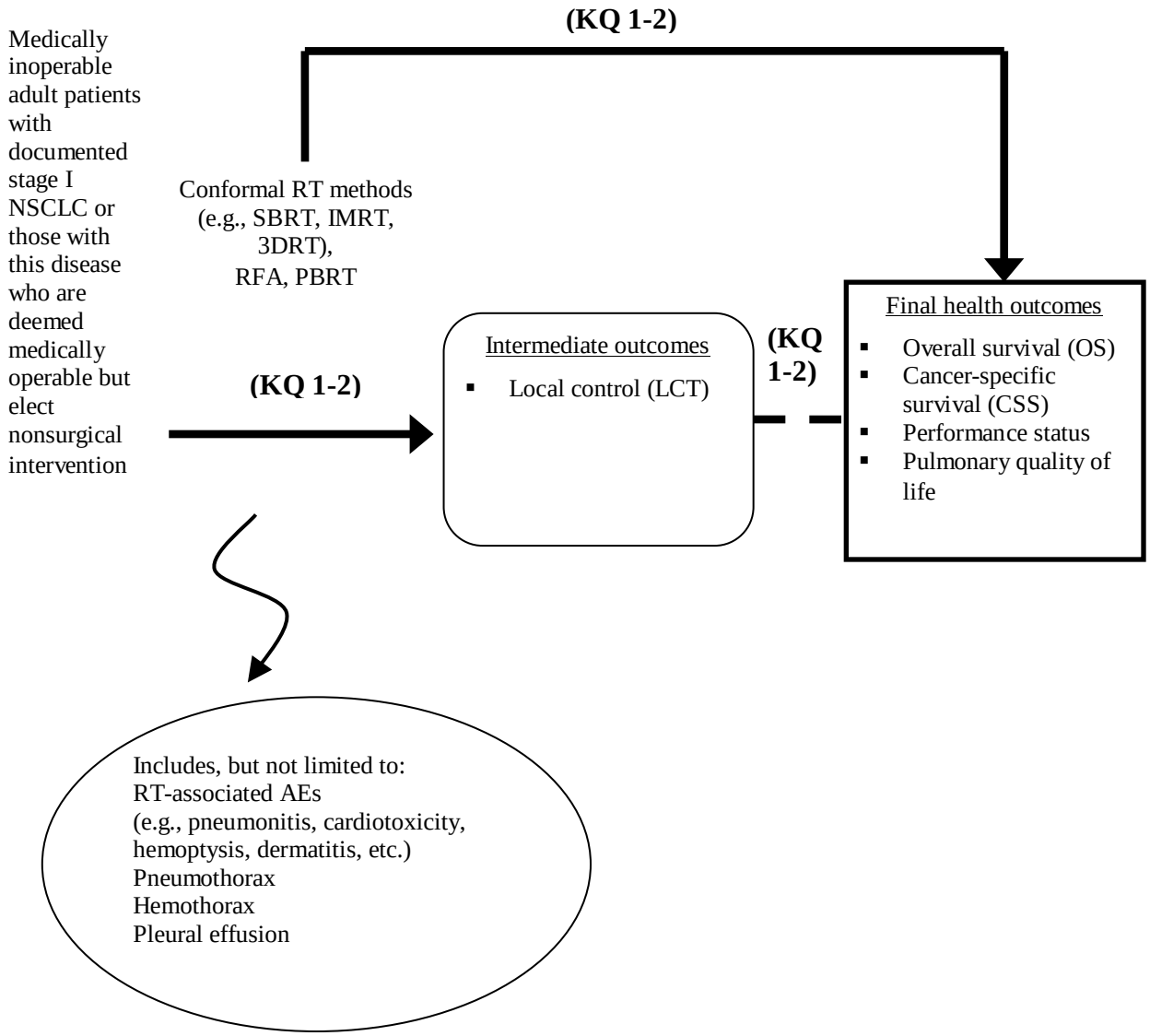
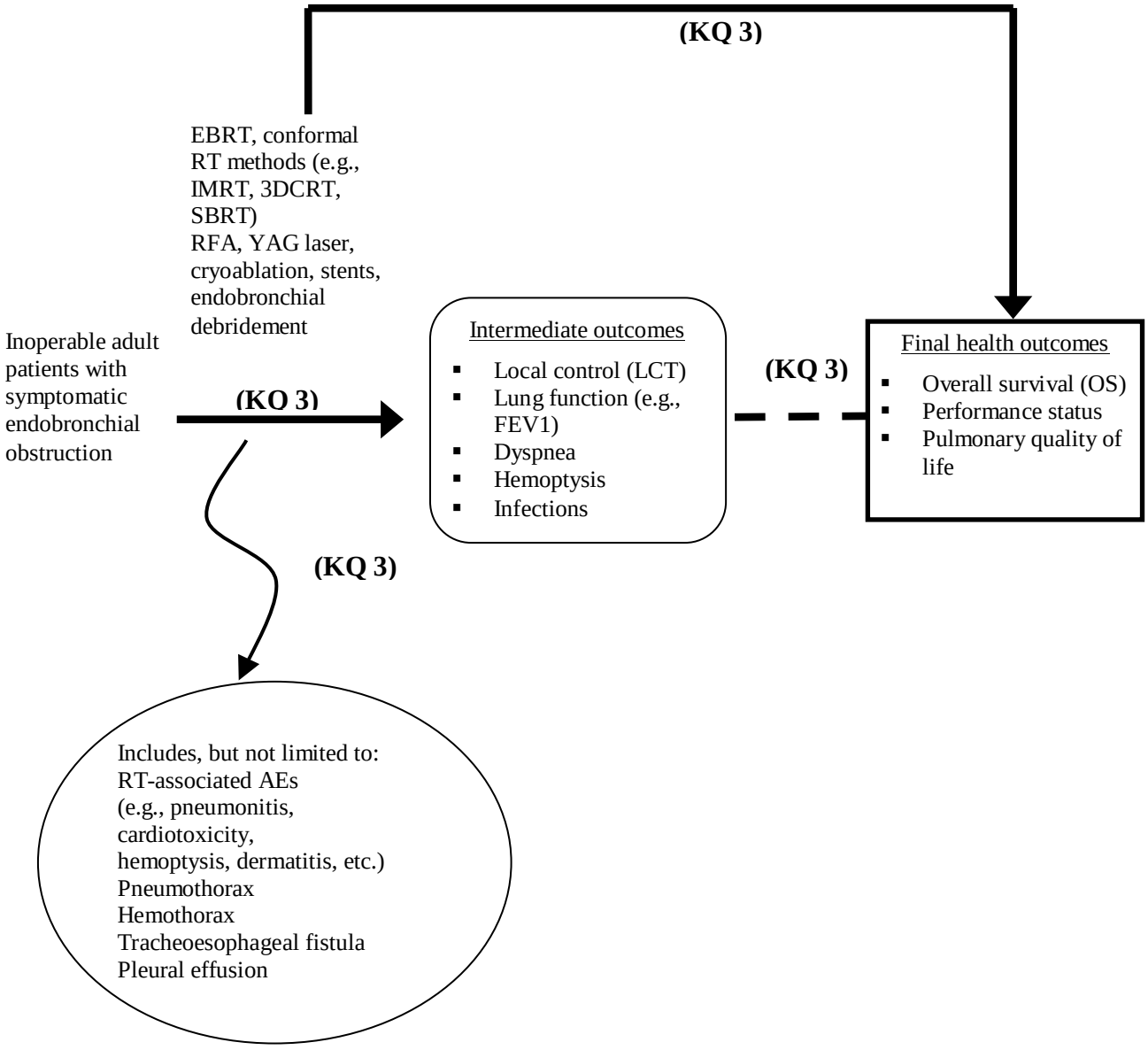


Figure 2. Analytical framework for comparative effectiveness of local curative or palliative therapies for adult patients (age 18 years or older) with symptomatic inoperable endobronchial obstruction due to NSCLC.



Key Question 1

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

Key Question 2

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

Key Question 3

- What are the comparative short- and long-term benefits and harms of local 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?

PICOTS Framework

Key Questions 1 and 2

Population(s)

Key Question 1:
Adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 and T2N0M0) non-small cell lung cancer who were not deemed surgical candidates because of the documented presence of contraindications to major surgery, for example, cardiac insufficiency, poor pulmonary function, presence of severe intercurrent illness, or poor performance status.

Key Question 2:
Adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 and T2N0M0) non-small cell lung cancer who would otherwise be deemed surgical candidates according to current clinical criteria but decline surgery

Interventions

- Conformal radiotherapy (RT) methods (including stereotactic body radiotherapy, three-dimensional conformal radiotherapy, intensity-modulated radiotherapy)
- Proton beam radiotherapy (PBRT)
- Radiofrequency ablation (RFA)

Comparators

Key Questions 1 and 2

- Interventions were compared with each other as appropriate and noted above.

Outcomes

Key Questions 1 and 2

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

Timing

- The relevant periods occur at the time of treatment through followup over months (palliation) or years (overall survival).

Settings

- Inpatient and outpatient

Key Question 3

Population

Adult patients (age 18 years or older) with NSCLC with endoluminal obstruction of the trachea, main stem, or lobar bronchi and recurrent or persistent thoracic symptoms such as hemoptysis, cough, dyspnea and postobstructive pneumonitis, who were treated with curative or palliative intent.

Interventions

- Conventional 2D external beam radiotherapy (2DRT)
- Conformal radiotherapy methods (including stereotactic body radiotherapy, three-dimensional conformal radiotherapy, intensity-modulated radiotherapy)
- Brachytherapy
- Radiofrequency ablation
- Cryoablation
- Laser therapy
- Endobronchial debridement and stents
- Electrocautery
- Combinations were considered, for example endobronchial debridement plus a stent, compared with debridement alone; or, combination of 2DRT with brachytherapy compared with RT alone.

Comparators

- Interventions were compared with each other as appropriate and noted above.

Outcomes

- Final health outcomes: Overall survival (OS), performance status, pulmonary quality of life
- Intermediate outcomes: Local control (LCT), lung function (e.g., forced expiratory volume [FEV1]), symptom relief (e.g., dyspnea, hemoptysis), respiratory tract infection

- Adverse outcomes: Includes, but not limited to, RT-associated AEs (e.g., pneumonitis, cardiotoxicity, hemoptysis, dermatitis, etc.), non-RT associated AEs (e.g., pneumothorax, pleural effusion, transesophageal fistula, pericardial effusion)

Timing

- The relevant periods occur at the time of treatment through followup over months (palliation) or years (overall survival).

Settings

- Inpatient and outpatient

Organization of This Report

The following chapters of this CER present the Methods used for preparation, including the search strategy used to identify the published and unpublished evidence relevant to Key Questions, as well as the processes used to systematically review and assess individual clinical studies for inclusion or exclusion, accompanied by relevant data extracted from these articles and compiled into evidence tables. The Results chapter is structured to address the Key Questions in the order presented above, including summary tables that compile the evidence used in the report, an analysis of the quality and risk of bias of individual clinical studies, key points of evidence for the patient-important clinical outcomes, and a detailed synthesis of compiled evidence for each outcome according to Key Question. A subsequent Discussion section addresses the key findings and the strength of evidence for all Key Questions using standard systematic review procedures outlined by AHRQ, a discussion of how the findings relate to or compare to existing standards, and the applicability of the body of evidence for each Key Question in terms of the PICOTS framework. The Discussion section also addresses implications for policy decisions, in the context of limitations of the systematic review processes used and the evidence itself. The CER concludes with a chapter devoted to outlining the gaps in the available evidence base for each Key Question, and a Conclusions section that interprets the findings in the context of all considered factors.

The electronic search strategy for this Report is located in Appendix A. A list of excluded studies with reasons for exclusion is provided in Appendix B. Data abstraction tables for each Key Question can be found in Appendix C.

Methods

This chapter describes the methods used to produce this comparative effectiveness review (CER). Methodological practices followed in this review were derived from the *Methods Guide for Effectiveness and Comparative Effectiveness Review*[30] (hereafter *Methods Guide*) and its subsequent updates. The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[82] All methods and analyses were determined *a priori* except as specified in the listed amendments (below).

Topic Refinement and Review Protocol

The topic for this Report and preliminary Key Questions arose through a public process involving the public and various stakeholder groups. Initially a panel of Key Informants gave input on draft Key Questions. Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the Report and have not reviewed the Report, except as given the opportunity to do so through the peer or public review mechanism. Key Informants had to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. The AHRQ Task Order Officer (TOO) and the EPC worked to balance, manage, or mitigate any potential conflicts of interest identified.

The Key Questions were posted on AHRQ's website for public comment on October 5, 2011 for 4 weeks and revised as necessary. The EPC drafted a protocol for the CER and recruited a panel of technical experts who provided input throughout the development of the review, but were not involved in evidence analysis or drafting the report. The draft protocol was reviewed by the technical experts, and AHRQ personnel including the Task Order Officer for the project. The final protocol was posted to AHRQ's website on February 22, 2012.

Literature Search Strategy

Search Strategy

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

- MEDLINE®
- EMBASE®
- Cochrane Controlled Trials Register

The search was limited to English language studies based on the following rationale. First, there is evidence to suggest that language restrictions do not change results of systematic review for conventional medical interventions.[31] Second, input from the Technical Expert Panel 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 language 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 searches were limited to studies of human subjects and those published in English. The full search strings and strategies can be found in Appendix A.

Grey Literature

Grey literature was sought by searching for clinical trials (Clinicaltrials.gov), Food and Drug Administration website, and relevant conference abstracts (American Society of Clinical Oncology, and American Society for Radiation Oncology). We limited the grey literature search until 2010. We reviewed Scientific Information Packets provided by the Scientific Resource Center. Study authors were not contacted for unpublished results. Our goal was to include only Phase III RCTs that we had not identified in our main electronic or hand searches.

Study Selection

Inclusion Criteria

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

Key Questions 1 and 2

1. Study included medically inoperable NSCLC stage I patients (T1N0M0 and T2N0M0) or medically operable NSCLC stage I patients (T1N0M0 and T2N0M0) who refuse surgery and
2. Such patients received only 1 of the following interventions
    - Conformal radiotherapy methods (including stereotactic body radiotherapy, three-dimensional conformal radiotherapy, intensity-modulated radiotherapy)
    - Proton beam therapy
    - Radiofrequency ablation
3. Study reported data on one or more of the following outcome data for such patients
    - Survival outcome (overall survival [OS] or cancer-specific survival [CSS])
    - Local control ([LCT}, an outcome defined as the arrest of cancer growth at the site of origin)
    - QOL
    - Adverse events

Key Question 3

1. Study included NSCLC patients of any stage with an endoluminal obstruction and
2. Such patients received 1 or more of the following interventions
    - Conformal radiotherapy methods (including stereotactic body radiotherapy, three-dimensional conformal radiotherapy, intensity-modulated radiotherapy)
    - Conventional 2D external beam radiotherapy
    - Proton beam therapy
    - Radiofrequency ablation
    - Brachytherapy
    - Cryoablation

    - Laser Therapy
    - Electrocautery
    - Endobronchial debridement and stents, and
3. Study reported data on one or more of the following outcome data for such patients
    - Survival outcome (overall survival or disease specific survival)
    - Local control (an outcome defined as the arrest of cancer growth at the site of origin)
    - Symptom relief
    - QOL
    - Adverse events

Exclusion Criteria

- Editorials, commentaries, abstracts, animal studies, case report, non-English language, diagnostic accuracy study
- On advice of our TEP, primary studies published prior to January 1, 1995 were excluded, to assure we considered current techniques and methods.
- Other reasons used to exclude studies were based on an assessment of the presence of duplicate patients in more than one paper; in that event we included the article that included the same patients at longest follow up, cross-indexing that in the abstraction tables.
- No definitive surgical intervention was considered for any KQ.
- For KQ 1 and 2, we planned to compare single interventions, for example two different conformal RT methods, or RFA compared with a conformal RT method. We excluded studies that mentioned the use of any post-intervention systemic or local therapy but did not define the therapy or disaggregate the clinical outcomes of recipients.

A list of excluded primary studies and reasons for exclusion are provided in Appendix B.

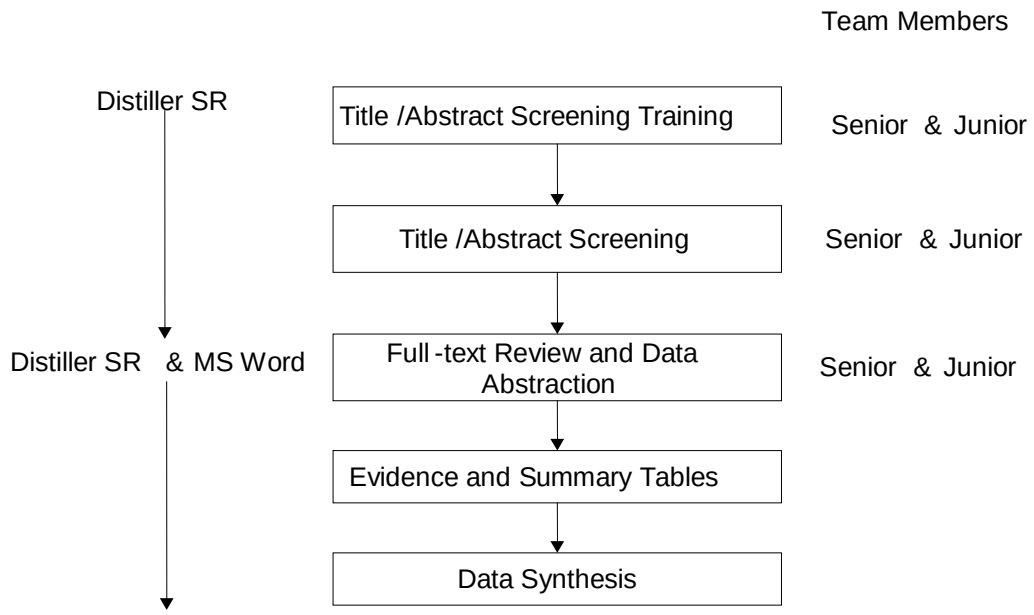
Study Selection

Electronic search results were transferred to EndNote® and subsequently into Distiller SR® for study screening and selection. Using the study-selection criteria (outlined above in this section) for screening titles and abstracts, each citation was marked as: 1) eligible for review as full-text articles; 2) ineligible for full-text review. At least one training set (n=100) of representative titles and abstracts for each KQ was examined initially by all team members to assure uniform application of screening criteria. A subsequent set was assessed to establish concordance among the team. Title and abstract screening was performed by 2 junior and 1 senior level team members. A study was excluded only when both team members made independent decision to exclude it. In case of disagreement, the team lead adjudicated in consensus with all team members. A record of the reason for exclusion of each paper retrieved was kept in the Distiller SR database. While a paper may be excluded for multiple reasons, only one was recorded.

A test set of three papers relevant to the three KQs was evaluated in full-text by junior and senior team members, including the team leader, to ensure selection criteria were applied correctly. Subsequently, two junior team members and the team lead reviewed full-text articles independently to determine their inclusion in the systematic review. Team meetings were held

regularly to discuss progress and to ensure the team leader was aware of difficulties or problems in this process. The process is shown schematically in Figure 3.

Figure 3. Schematic for data management



Data Extraction & Management

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 Distiller SR®. A data abstraction guide was created that detailed the process of abstraction of data and definition of key data elements to ensure accuracy and consistency in data abstraction procedure across the team. 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 reviewer reviewed the articles and evidence tables for accuracy. Disagreements were resolved by discussion, and if necessary, by consultation with a third reviewer.

Data Elements

- Study Attributes
    - Design
    - Author
    - Country
    - Year
    - Study start date
    - Study end date
    - Study setting
    - Treatment setting
    - Institution setting(s):
    - Criteria for staging:

    - Conflict of interest
    - Study funding
- Patient characteristics
    - Patients Enrollment numbers
    - Lost to followup/Excluded
    - Inclusion/Exclusion Criteria
    - Stage Distribution
    - Tumor Location
    - Tumor Histopathology
    - Age
    - Women
    - Race
    - Co-morbidities
    - Performance status
    - Histopathology confirmation
- Study Objective
- Primary outcome
- Secondary outcome(s)
- List of Outcome(s)
- Cause of death
- Length of followup
- Treatment details
    - Intervention name
    - Vendor name
    - Dose/frequency/details
    - Technical details
    - Treatment Intention
- Follow-up and Evaluation Criteria
- Study Outcomes
    - Survival
        - Overall survival
        - Disease specific survival
        - Local control
    - Lung Outcomes
        - Lung function
        - Obstructive symptoms
        - Quality of life
        - Performance status
        - Others
    - Adverse Events

Quality (Risk of Bias) Assessment of Individual Studies

In adherence with the *Methods Guide*,[30] the general approach to grading the risk of bias of individual comparative studies was performed by using a method used by the United States Preventive Services Task Force.[32] This approach is relevant to both randomized trials and

nonrandomized comparative interventions studies. Assessment of the quality of included nonrandomized comparative intervention studies by this approach was informed by a selection of items proposed by Deeks et al.[83] The quality of the abstracted studies was assessed by one reviewer, and examined by the senior lead.

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

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

Good. Meets all criteria; comparable groups are assembled initially and maintained throughout the study (followup at least 80 percent); 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 has been done for RCTs.

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

Our assessment of risk of bias in the included single-arm intervention studies was based on a set of study characteristics proposed by Carey and Boden.[33] These 8 criteria are as follows:

1. Clearly defined study questions
2. Well-described study population
3. Well-described intervention
4. Use of validated outcome measures

5. Appropriate statistical analyses
6. Well-described results
7. Discussion and conclusion supported by data
8. 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 8 Carey and Boden criteria mentioned above had to be met. For a fair quality assessment, 7 of 8 criteria had to be met. A study that met fewer than 7 of 8 criteria was rated as poor quality. These quality rankings for these studies can be found in Appendix C.

Data Synthesis

Given the lack of appropriate comparative studies for all KQs, this evidence review did not incorporate formal data synthesis involving meta-analysis. The quality of individual studies was assessed as outlined above, and the strength of the body of evidence for each KQ was evaluated as follows.

Strength of the Body 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 *Methods Guide* and is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[30, 32, 35] This system explicitly addressed 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 strength of evidence grade. Specific outcomes and comparisons that were rated were based on the evidence found in the literature review.

The process of grading a body of evidence[34] was as follows. A body of evidence represented by randomized trial(s) would have a starting strength of high. A body of evidence represented by non-randomized comparative studies would generally have a starting strength of low. The strength of evidence would then by reduced by one level if there was high risk of bias, inconsistency or unknown consistency, indirectness and imprecision. If the study was fatally flawed, the strength of evidence was reduced by two levels.

The strength of evidence could be raised by at least one level for each of the following if:

- There was a large effect
- There was a dose response
- All plausible confounding and bias would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed.

The grade of evidence strength was classified into the following four categories:

- **High.** High confidence that the evidence reflected the true effect. Further research was very unlikely to change our confidence in the estimate of effect.

- **Moderate.** Moderate confidence that the evidence reflected the true effect. Further research may have changed our confidence in the estimate of effect and may have changed the estimate.

- **Low.** Low confidence that the evidence reflected the true effect. Further research was likely to change our confidence in the estimate of effect and was 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.

Applicability

Applicability of findings in this review was assessed according to the AHRQ Comparative Effectiveness Methods Guide using the PICOS (Population, Intervention, Comparator, Outcome, Setting) framework.[30, 84, 85] Included studies were assessed for relevance against target populations, interventions and comparators of interest, and outcomes of interest.

Peer Review and Public Commentary

Peer reviewers will be invited to provide written comments on the draft Report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the Report will be considered by the EPC in preparation of the final draft of the report. Peer reviewers have not participated in writing or editing of the final Report or other products. The synthesis of the scientific literature presented in the final Report will not necessarily represent the views of individual reviewers. The dispositions of the peer review comments will be documented and published three months after the publication of the evidence Report.

Potential reviewers will have to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers cannot have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest will be able to submit comments on draft reports through the public comment mechanism.

Results

Introduction

Overview

This chapter presents the results of this comparative effectiveness review (CER) on local interventions for patients with non-small cell lung cancer (NSCLC) in three distinct settings. Key Question (KQ) 1 addresses interventions in patients with stage I disease but who are deemed medically inoperable secondary to the presence of comorbidities that preclude definitive resection. KQ2 addresses local intervention in patients with stage I disease who are deemed medically operable but refuse surgery. KQ3 addresses evidence for the use of local interventions in patients with symptoms secondary to an inoperable obstructive endoluminal NSCLC.

The results from the electronic literature search enumerate studies that were included and excluded from the review based on full-text examination. The latter are shown in Appendix B with reasons for their exclusion. The chapter is organized in order according to Key Questions 1, 2, and 3, by intervention. As stated in the Methods chapter, we did not perform a quantitative data synthesis for any KQ. We originally intended to report some outcome data in strata according to prognostic or other patient-related factors such as tumor stage, providing they were reported separately or could be inferred from the study in question. However, given the nature of the evidence base for KQs 1 and 2—single-arm studies—we did not stratify outcomes. We assessed the risk of bias of single-arm studies using the convention of Carey and Boden described in the Methods. For the KQ3 randomized trials, we used the United States Preventive Services Task Force (USPSTF) tool described in the Methods chapter to assess study quality and risk of bias.

Results of Literature Searches

Electronic Search

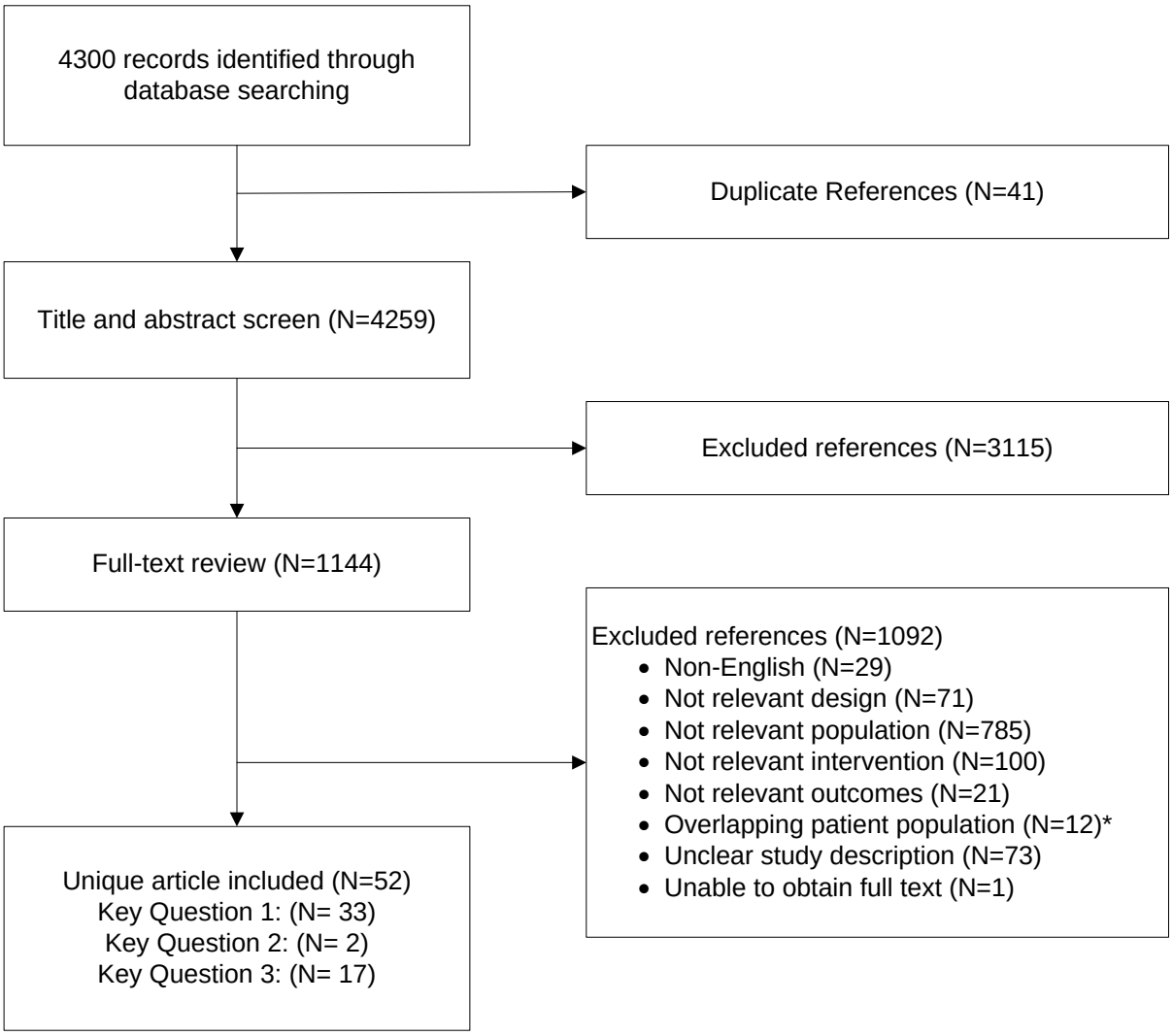
Out of a total 4,259 unique titles, we retrieved 1,145 for full-text screening. A total of 35 studies were included for KQ 1 and 2. All were single-arm design, prospective (n=13), retrospective (n=19) or not specified (n=1). Among the 17 papers included for KQ3 were five randomized trials, one nonrandomized comparative study, and 11 of prospective or retrospective single-arm design. Among all studies screened, 52 met the CER inclusion criteria. Two studies of stage I patients enrolled inoperable and operable patients and reported outcomes of those two groups separately.[37, 56] Therefore, those two studies appear in the results for KQ1 and KQ2, but were not double-counted in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram,[82] shown in Figure 4.

Grey Literature (Publication Bias)

Following an in-depth review of 759 potentially relevant abstracts in the American Society of Clinical Oncology, and the American Society and American Society for Radiation Oncology proceedings over the past two years, and other sources including Clinicaltrials.gov, we identified one randomized controlled trial (RCT) that met the criteria for inclusion based on our protocol. This study (NCT00020709) is a Phase III RCT of surgery versus stereotactic body radiotherapy

(SBRT) in patients with Stage IA NSCLC who were fit to undergo primary resection. This study was terminated due to poor recruitment and it is unknown if any observational data have been distributed elsewhere from this study. After a MEDLINE search of the NCT number and title, no results were discovered that could be linked to this trial. In examination of the U.S. Food and Drug Administration website and the Scientific Information Packets received from device manufacturers, we identified no additional randomized controlled studies that would affect our CER results.

Figure 4. PRISMA diagram for identified trials



*Overlapping patient population refers to the studies where same patients were included in more than one study. In all such cases, only one study was included to avoid over sampling. The decision to include the study was based upon nature of the study design (preference of RCT over observational study designs) and the clarity in reporting relevant patients and/or outcomes.

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

Description of Included Studies

Table 2 provides a summary of characteristics of 33 single-arm studies that met our selection criteria for KQ 1. Thirteen were described as being prospective.[36, 37, 47, 48, 50, 52, 57, 59, 86-89] Interventions for which evidence was available included sterotactic body radiotherapy (SBRT) (22 studies, total n=1413 patients) [40-61], 3DRT (7 studies, total n=240 patients),[86-92] proton beam radiotherapy (PBRT) (three studies, total n=144 patients)[36-38] and radiofrequency ablation (RFA) (1 study, n=19 patients).[39] More detailed information on the interventions is provided in Appendix C. Among all studies, patients were typically in their 70s, with median ages ranging from 67-81 years, and an overall range from 31-93 years. Reasons for medical inoperability among the patients included in those studies are shown in in Appendix C. They typically included the presence of pulmonary disease (chronic obstructive pulmonary disease), insufficient predicted posttherapy lung function, cardiovascular disease, and other comorbidities that in total preclude surgical resection. Sex distribution was uneven, with proportions of females ranging from 9-80 percent across studies. Karnofsky performance status (KPS) of enrollees ranged from 40-100 in 11 studies,[36, 40, 41, 43-46, 48, 55, 61, 87, 88] Eastern Cooperative Oncology Group (ECOG),[52-54, 58, 61, 86, 90, 91] World Health Organization (WHO)[47, 56], or European Organization for Research and Treatment of Cancer (EORTC)[38] KPS ranged from 0-3 across 11 studies. PS was not reported in 11 studies.[37, 39, 42, 49-51, 57, 59, 60, 89, 92] Fifteen studies (45 percent) reported 100 percent histological confirmation of NSCLC cell types.[36, 37, 40, 41, 46-49, 55, 86, 88, 90-92] The other eighteen (55 percent) reported less than 100 percent histological confirmation of patient tumors,[38, 39, 41-44, 48-53, 55-58, 60, 61, 88] with a median of 26 percent of patients deemed not to have histologically confirmed NSCLC out of these eighteen studies. Among the latter studies, evidence of a growing lesion at successive computedtomography (CT) examination with demonstration of 18F-fluorodeoxyglucose avidity were typically reported as supporting the presence of NSCLC.

Key Points

- All evidence included in this report for KQ1 is from single-arm studies. No evidence is available from any type of direct comparative study of one intervention versus another or versus a placebo or sham procedure.
- Evidence from 33 single-arm studies is insufficient to form conclusions about the comparative benefits or harms of SBRT (22 reports), 3DRT (seven reports), PBRT (three reports) and RFA (one report) in medically inoperable patients with stage I NSCLC.
- The evidence comprises direct outcomes OS and CSS; an indirect outcome, LC; and, radiation-associated toxicities.
- Overall, post-treatment toxicities were not common across studies. No relative trend can be detected among interventions.
- It is unknown whether the limited evidence on adverse events reflects absence, or that the investigators did not systematically collect data or report them.

Table 2. Summary of characteristics for studies that address Key Question 1

Treatment	Study	Design (Quality)[33]	N	Intervention Details	Histopathology Confirmation	Age, years	% Female
3DRT	Bogart et al, 2010, USA[86]	Prospective (Poor)	39	70 Gy 17-29 frs	Yes	75 (48-87)	53%
	Bradley et al, 2003, USA[87]	Prospective (Fair)	56	70 Gy 5 frs	Yes	73 (52-90)	57%
	Campeau et al, 2009, Australia[90]	Retrospective (Fair)	34	60 Gy 30 frs	Yes	81 (54-88)	41%
	Graham et al, 2006, Australia[91]	Retrospective (Fair)	N: 39 (100%) Inoperable: 36 (92%) Refused or NR: 3 (8%)	65 Gy 35 frs Concurrent end-phase boost	Yes	72[B] (53-84)	38%
	Jimenez et al, 2010, Spain[92]	Retrospective (Poor)	47	79Gy 44 frs (calculated)	Yes	68±10	23%
	Mirri et al, 2009, Italy[88]	Prospective (Poor)	15	40 Gy BED: 72 Gy 5 frs	No (27%)	76[B]	NR
	Narayan et al, 2004, USA[89]	Prospective (Poor)	13	92 or 103 Gy 44-49 frs (calculated)	Yes	67±18	9
PBRT	Bush et al, 2004, USA[36]	Prospective (Good)	N: 68 (100%) Inoperable: 63 (93%) Refused: 5 (7%)	51 CGE 10 frs 60 CGE 10 frs	Yes	72 (52-87)	56
	Iwata et al, 2010, Japan[37]	Prospective (Good)	N: 57 (100%) Inoperable: 29 (51%) Refused: 28 (49%)	80 or 60 Gy BED: 96- 112 Gy 20 frs	Yes	76 (48-89)	29%
	Nakayama et al, 2010, Japan[38]	Retrospective (Poor)	N: 55 (100%) Inoperable: 52 (94%) Refused: 3 (6%)	66-73 GyE, 10-22 frs	No (12%)	74±9	26%
RFA	Pennathur et al, 2007, USA[39]	Retrospective (Good)	19	RF3000: power 5-10W increments until system impedance > 400 ohm RITA: power 35-50 W, target temperature 90 degrees C	Yes	78 (68-88)	58%
SBRT	Andratschke et al, 2011, Germany[40]	Retrospective (Poor)	92	24-45 Gy 3-5 frs	Yes	75 (53-93)	30
	Baumann et al, 2006, Denmark[42]	Retrospective (Poor)	N: 141 (100%) Inoperable: 136 (96%) Refused: 5 (4%)	30-48 Gy 2-4 frs	No (24%)	74 (56-90)	51
	Baumann et al, 2009, Denmark [41]	Retrospective (Good)	N: 57 (100%) Inoperable: 56 (99%) Refused: 1 (2%)	45 Gy BED: 112 Gy	No (33%)	75 (59-87)	54
	Burdick et al, 2010, USA[43]	Retrospective (Fair)	72	50-60 Gy 3-10 frs	No (32%)	73 (52-90)	NR

Treatment	Study	Design (Quality)[33]	N	Intervention Details	Histopathology Confirmation	Age, years	% Female
	Coon et al, 2008, USA[44]	Retrospective (Poor)	N: 26 (100%) Inoperable: 24 (92%) Refused: 2 (8%)	60 Gy 3 frs	No (38%)	76.5[A]	NR
	Dunlap et al, 2010, USA[45]	Retrospective (Fair)	N: 40 (100%) Inoperable: 37 (92%) Refused: 3 (8%)	30-60 Gy BED: 78-180 Gy 3-5 frs	Yes	73 (54-87)	NR
	Fritz et al, 2008, Germany[46]	Retrospective (Fair)	N: 40 (100%) Inoperable: 37 (92%) Refused: 3 (8%)	BED: 100 Gy	Yes	74 (59-82)	20
	Kopek et al, 2009, Denmark[47]	Prospective (Good)	88	45 or 68 Gy 3 frs	Yes	73 (47-88)	49
	Nyman et al, 2006, Sweden, [48]	Prospective (Fair)	45	45 Gy 3 frs	No (20%)	74[B] (58-84)	44
	Olsen et al, 2011, USA[49]	Retrospective (Poor)	N: 130 (100%) Inoperable: 117 (90%) Refused: 13 (10%)	45-54 Gy 3-5 frs	No (15%)	75 (31-92)	50
	Palma et al, 2011, Netherlands[50]	Prospective (Poor)	N: 176 (100%) Inoperable: 169 (96%) Refused or NR: 7 (4%)	54-64 Gy 3-8 frs	No (68%)	70 (47-86)	45
	Pennathur et al, 2009, USA[51]	Retrospective (Fair)	21	20-60 Gy BED: 60-70 Gy 1-3 frs	No (5%)	71 (61-85)	57
	Ricardi et al, 2010, Italy [52]	Prospective (Poor)	N: 62 (100%) Inoperable: 56 (90%) Refused: 6 (10%)	45 Gy BED: 124 Gy 3 frs	No (36%)	74[B] (53-83)	16
	Scorsetti et al, 2007, Italy[53]	NR (Poor)	43	20-32 Gy BED: 40-117 Gy 2-4 frs	No (5%)	75 (52-90)	21
	Song et al, 2009, Korea[54]	Prospective (Good)	N: 32 (100%) Inoperable: 31 (97%) Refused: 1 (3%)	40-60 Gy 3-4 frs	Yes	72 (58-89)	19
	Stephans et al, 2009, USA[55]	Retrospective (Good)	86	50-60 Gy 3-5 frs	No (29%)	73 (40-90)	56
	Takeda et al, 2009, Japan[56]	Retrospective (Fair)	N: 63 (100%) Inoperable: 49 (78%) Refused: 14 (22%)	50 Gy 5 frs	No (17%)	78 (56-91)	36
	Taremi et al, 2011, Canada[57]	Prospective (Fair)	108	48-60 Gy 3-10 frs	No (25%)	73 (48-90)	51
	Turzer et al, 2011, Norway[58]	Retrospective (Fair)	N: 36 (100%) Inoperable: 35 (97%) Refused: 1 (3%)	45 Gy 3 frs	No (26%)	74 (54-85)	64
	Vahdat et al, 2010, USA[59]	Prospective (Poor)	20	42-60 Gy 3 frs	Yes	75 (64-86)	80
	van der Voort van Zyp et al, 2009,	NR (Poor)	N: 70 (100%) Inoperable: 65 (93%)	36-60 Gy 3 frs	No (49%)	76 (54-90)	NR

Treatment	Study	Design (Quality)[33]	N	Intervention Details	Histopathology Confirmation	Age, years	% Female
	Netherlands[60]		Refused: 5 (7%)				
	Videtic et al, 2010, USA[61]	Retrospective (Fair)	26	50 Gy 5 frs	No (29%)	74 (49-88)	50

3DRT: three dimensional radiotherapy; BED: biologically effective dose; CGE: cobalt gray equivalent; FRS: fractions; Gy: grays; GyE: gray equivalent; N: total sample size of the study; NR: not reported; PBRT: proton beam radiotherapy; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy

Values are mean (±SD) or median (range) unless specified

[A] Median

[B] Mean

Detailed Synthesis

All survival outcomes abstracted for this CER are compiled in Appendix C. In Table 3, we have aggregated evidence from the largest number of studies with the longest followup periods.

Table 3. Survival and local control outcomes for local interventions in medically inoperable patients with stage I NSCLC

Intervention	Reported overall survival rates (number of patients)[Ψ]	Reported cancer-specific survival rates (number of patients) [Ψ]	Reported local control rates (number of patients) [Ψ]
3DRT	3-years: 33-61% 4 studies[87-89, 92] (n = 131) 5-years: 30% 1 study[91] (n = 36)	3-years: 48%, 51% 2 studies[87, 89] (n = 69) 5-years: 53% 1 study[91] (n = 36)	3-years: 63%, 72% 2 studies[87, 88] (n = 71) 5-years: NR
SBRT	3-years: 52-77% 6 studies[41, 42, 46, 52, 56, 61] (n = 360) 5-years: 17-30% 5 studies[40, 42, 47, 48, 50] (n = 530)	3-years: 57-94% 6 studies[41, 42, 45, 46, 52, 56] (n = 371) 5-years[40, 42, 48]: 40-48% 3 studies[47, 51, 53] (n = 273)	3-years: 81-94% 5 studies[41, 46, 50, 52, 61] (n = 344) 5-years: 83% 1 study[40] (n = 92)
PBRT	3-years: 44%, 65% 2 studies[36, 37] (n = 92)	3-years: 72% 1 study[36] (n = 63)	3-years: 74% 1 study[36] (n = 63)
RFA	2-years: 68% 1 study[39] (n = 19)	83% at FU 1 study[39] (n = 19)	58% at FU 1 study[39] (n = 19)

3DRT: three dimensional radiotherapy; FU: followup; n: number; NSCLC: non-small cell lung cancer; NR: not reported; PBRT: proton beam radiotherapy; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy
[Ψ] Number of patients represents only inoperable

The evidence summarized in Table 3 reflects single-arm studies that report direct outcomes OS and CSS and an indirect outcome, LCT. Rates for OS, CSS, and LCT for SBRT at 3-years followup suggest a possible trend toward exceeding those reported with 3DRT. However, the ranges reported overlap. Furthermore, as this evidence comprises single-arm studies with no direct comparisons, conclusions are precluded. The nature of the evidence – no comparative studies - does not support making indirect comparisons among interventions.

Intervention-Associated Adverse Events

Intervention-related toxicities reported in at least 2 percent of the study population are shown in Appendix C. Toxicities enumerated are those reported as grade 2 or greater (moderate) according to accepted scales, for example, the NCI Common Toxicity Criteria for Adverse Events (CTCAE), or the World Health Organization scale. They are all similar with respect to their grades and definitions. For KQ 1 and 2, these included radiation-associated pneumonitis and pulmonary toxicity, dyspnea, esophagitis, thoracic wall pain, pericardial or pleural effusion, bronchial stricture, and rib fracture. Rib fractures were reported in 9 (41 percent) SBRT studies[40-42, 45-48, 50, 52] and one PBRT study.[38] One death was attributed to grade 5 pericardial effusion at 3 months posttreatment in a 3DRT study.[88] A second death was attributed to grade 5 hemoptysis in an SBRT study.[54] Complications associated with RFA included pneumothorax and prolonged air leak from the lung.

As shown in Table 4, no relative differential in reporting toxicities is evident among or across interventions, with the possible exception of rib fractures mentioned above.

Table 4. Studies reporting intervention-associated toxicities in stage I medically inoperable NSCLC patients

Toxicity	SBRT (%)	3DRT (%)	PBRT (%)	RFA (%)
None	2 (10)	2 (29)	1 (50)	0
Grade 2	9 (41)	3 (43)	1 (50)	NA
Grade > 2	13 (43)	2 (29)	1 (50)	NA
Rib Fracture	9 (41)	0	1 (50)	NA
Mortality	1 (5)	0	1 (50)	(100)

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

Overall, post-treatment toxicities were not commonly reported across studies in the body of evidence. It is unknown whether the limited evidence on adverse events reflects absence, or that the investigators did not systematically collect data or report them.

Key Question 2. Comparative Effectivness of Local Interventions for Stage I NSCLC in Medically Operable Patients

Table 5 provides a summary of characteristics of 4 single-arm studies that address KQ 2. It includes two studies on SBRT that enrolled only operable patients.[62, 63] It also shows data from one each on PBRT[37] and SBRT[56] that enrolled inoperable and operable patients and reported outcomes separately. Data on the inoperable patients from the latter two reports are shown in Table 2 under KQ 1 above. Overall, patients were typically in their mid-70s, with median ages ranging from 74-76 years, and overall range from 43-91 years. Sex distribution was uneven, with proportions of males ranging from 57-72 percent across studies. ECOG and WHO PS ranged from 0-3 across studies. Two studies reported 100 percent histological confirmation of NSCLC cell type[37, 63] Additional details on the included studies are provided in Appendix C.

Table 5. Summary of characteristics for studies that address Key Question 2

Treatment	Study	Design (Quality)[33]	N	Intervention Details	Histopathology Confirmation	Age, years (range)	Female	Performance Status
PBRT	Iwata et al, 2010, Japan[37]	Prospective (Good)	N: 57 (100%) Inoperable: 29 (51%) Refused: 28 (49%)	80 or 60 Gy BED: 96- 112 Gy 20 frs	Yes	76 (48-89)	23 (29%)	NR
SBRT	Lagerwaard et. al, 2011, Netherlands[62]	Retrospective (Poor)	177	60 Gy BED > 100 Gy for all frs 3, 5, or 8 frs	No	76 (50-91)	76 (43%)	WHO < 3: 177 (100%)
SBRT	Onishi et. al, 2011, Japan[63] (longer FU to Onishi et. al, 2007)[93]	Retrospective (Good)	87	45-72 Gy BED:116(100-141) Gy 3-10 frs	Yes	74 (43-87)	24 (28%)	ECOG 0: 51 (59%) 1: 30 (34%) 2: (7%)
SBRT	Takeda et al, 2009, Japan[56]	Retrospective (Fair)	N: 63 (100%) Inoperable: 49(78%) Refused: 14 (22%)	50 Gy 5 frs	No	78 (56-91)	23 (36%)	WHO ≤ 2: 63 100%

3DRT: three dimensional radiotherapy; BED: biologically effective dose; ECOG: Eastern Cooperative Oncology Group; FRS: fractions; Gy: grays; NR: not reported; PBRT: proton beam radiotherapy; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy; WHO: World Health Organization

Key Points

- All evidence included in this Report for KQ1 is from single-arm studies. No evidence is available from any type of direct comparative study of one intervention versus another or versus a placebo or sham procedure.
- Evidence from 33 single-arm studies is insufficient to form conclusions about the comparative benefits or harms of SBRT (22 reports), 3DRT (7 reports), PBRT (3 reports) and RFA (1 report) in medically inoperable patients with stage I NSCLC.
- The evidence comprises direct outcomes OS and CSS; an indirect outcome, LC; and, radiation-associated toxicities.
- Overall, post-treatment toxicities were not common across studies. No relative trend can be detected among interventions.
- It is unknown whether the limited evidence on adverse events reflects absence, or that the investigators did not systematically collect data or report them.

Detailed Synthesis

Appendix C shows survival and local control outcomes with PBRT or SBRT in four studies relevant to KQ2. Survival outcomes were not reported across the studies.

In Table 6, survival outcomes are shown for each intervention.

Table 6. Survival and local control outcomes for local interventions in medically operable patients with stage I NSCLC

Intervention	Reported overall survival rates (N)	Reported cancer-specific survival rates (N)	Reported local control rates (N)
PBRT	3-years: 80% 1 study[37] (N = 28)	NR	NR
SBRT	3-years: 85%, 91% 2 studies[56, 62] (N = 191) 5-years: 70% 1 study[63] (N= 87)	3-years: 91% 1 study[56] (N = 14) 5-years: 76% 1 study[63] (N = 87)	3-years: 93% 1study[62] (N = 177) 5-years: 87% 1 study[63] (N= 87)

N: represents number of patients who were operable but refused surgery; NSCLC: non-small cell lung cancer; PBRT: proton beam radiotherapy; SBRT: stereotactic body radiotherapy

The evidence summarized in Table 6 above comprises single-arm studies that report direct outcomes OS and CSS and an indirect outcome, LCT. No direct comparative evidence is available to suggest any relative difference between the technologies in OS, CSS or local control rates.

Intervention-Associated Adverse Events

Appendix C shows intervention-related grade 2 or greater toxicities reported in at least 2 percent of the study population. Toxicities enumerated included radiation-associated pneumonitis and pulmonary toxicity, dermatitis, and rib fracture. Rib fractures were reported in 2 (67 percent) SBRT studies[62, 63] and in the PBRT study.[37] The toxicity reporting criteria for each study (when provided by the authors) are shown in Appendix C. Definitions used to grade toxicities vary, which further complicates any possible assessment.

Table 7 shows the distribution of reporting post-treatment toxicities across studies.

Table 7. Studies reporting intervention-associated toxicities in stage I medically operable NSCLC patients

Toxicity	SBRT (%)	PBRT (%)
None	0	0
Grade 2	2 (67)	1 (100)
Grade > 2	3 (100)	1 (100)
Rib Fracture	2 (67)	1 (100)
Other	NR	NR

NR: not reported; PBRT: proton beam radiotherapy; SBRT: stereotactic body radiotherapy

No relative trend in reporting toxicities can be discerned among interventions. It is unknown whether the limited evidence on adverse events reflects absence, or that the investigators did not systematically collect data or report them.

Risk of Bias For Individual Studies Addressing KQ1 and KQ2

We used the convention described by Carey and Boden[33] to assess the risk of bias of individual single-arm studies included to address KQ 1 and KQ2 (see Methods chapter). Our ratings of good, fair and poor are shown in Table 8. Good studies within this class met 8 of 8 criteria ("yes"); fair studies met 7 of 8 criteria, and poor studies met fewer than 7 criteria.

Among 35 single-arm studies, all reported the use of validated outcomes. According to the system we applied, study quality was most often downgraded from good because authors did not acknowledge the funding source in 22 (63 percent).[38, 42-46, 48, 49, 51-53, 56, 58-62, 87, 88, 90-92] In nine (26 percent) [38, 40, 49, 50, 52, 59, 88, 89, 92] of 35 studies, it was unclear whether or not the conclusions and discussion were supported by the data. Eight studies (23 percent)[49, 50, 57, 59, 60, 86, 88, 89] did not adequately describe the study population. Five (14 percent) [38, 59, 88, 89, 92] did not describe results well. Three (9 percent) [38, 62, 86] did not adequately describe the intervention. Three (9 percent) [40, 44, 88] did not report the use of appropriate statistical analysis. It is apparent that excepting failure to report a funding source, there was no consistent reason an individual study was downgraded.

Table 8. Carey and Boden quality rating summary

KQ (number of studies)	Good (8 of 8 "yes")	Fair (7 of 8 "yes")	Poor (< 7 of 8 "yes")
KQ1 (33)	7 (21%)[36, 37, 39, 41, 47, 54, 55]	12 (37%)[43, 45, 46, 48, 51, 56-58, 61, 87, 90, 91]	14 (42%)[38, 40, 42, 44, 49, 50, 52, 53, 59, 60, 86, 88, 89, 92]
KQ 2 (2)	1 (50%)[63]	NR	1 (50%)[62]
Total	8 (23%)	12 (34%)	15 (43%)

KQ: key question

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

Overview

This section describes the literature that evaluates the efficacy and safety of local therapies for palliation or treatment of endobronchial NSCLC. After an overview of the literature, the results are described for outcomes in three categories: outcomes related to obstructive symptom resolution, survival outcomes, and safety outcomes. Improvement in obstructive symptoms was the primary outcome of interest because palliative interventions are most proximately expected to have an impact on obstructive symptoms. We specifically looked for resolution or improvement in dyspnea, cough, hemoptysis, and pneumonitis and abstracted all other symptoms in the "other" category. In addition, we also abstracted survival outcomes that included overall survival (reported both as median overall survival and time specific survival whenever that was available), disease specific survival and local control. Among the outcomes related to treatment-related toxicities, we focused on hemoptysis, pneumothorax and radiation bronchitis. We only abstracted toxicities that were grade 2 or greater or necessitated an active intervention or considered serious by the authors/abstractors.

Overall, 17 studies were abstracted for this review. The evidence base consisted of six comparative studies[64-69] and 11 noncomparative studies.[94-104] Overall data for these studies is presented in Appendix C. Table 9 and Table 22 summarize the comparative and noncomparative studies reviewed for Key Question 3, respectively.

Study Characteristics of Comparative Studies

Among the six comparative studies that address KQ 3, five were RCTs and 1 was a retrospective nonrandomized comparative study. A total of 342 patients were randomized in these six studies[64-69] that compared six distinct treatment combinations. Additionally, we did not report data for 1 RCT[75] as it reported cumulative outcomes data for three different endobronchial treatments. The detailed outcomes related to symptom improvement, survival and adverse effects for all six comparative studies are presented in Appendix C. All six studies included patients with a histologically confirmed NSCLC. Four studies[64, 65, 68, 69] reported staging of lung cancer patients but only one study[65] reported the criteria used for staging NSCLC. The duration of the study enrollment period was reported by four studies[64, 66, 67, 69] and ranged from 2 to 4 years. Three studies[64, 66, 67] were conducted in an out-patient setting; one[69] was conducted in the inpatient setting and for two studies[65, 68] a setting was not reported. Four[64, 67-69] were single-center studies while the remaining two[65, 66] were multicenter studies. Four studies[66-69] did not state whether there existed a conflict of interest or not, while the remaining two studies[64, 65] stated no conflict of interest. Three studies[66, 67, 69] did not state the source of funding while one each was manufacturer sponsored,[68] professional scientific society sponsored[65] and investigator initiated.[64]

All six[64-69] comparative studies were rated as poor quality, five studies[64-67, 69] reported data on symptom relief, five studies[64-67, 69] reported survival data, two studies reported QOL data[64, 66] and six studies[64-69] reported data related to treatment-related toxicity. Detailed characteristics of patients included in the six studies are summarized in Table 10.

Table 9. Overview of Comparative Studies of Local Endobronchial Therapies

Treatment	Author, Year	Design	N	GQ	FQ	PQ	OS	DSS	LCT	SC	QOL	TOX
BCHY + EBRT vs. BCHY alone	Mallick-2006, India[64]	RCT	45			•				•	•	•
BCHY + EBRT vs. EBRT alone	Langendjik-2001, Netherlands[65]	RCT	98			•	•			•		•
BCHY vs. EBRT	Stout-2000, UK[66]	RCT	108			•	•			•	•	•
Laser + BCHY vs. laser alone	Chella-2000, Italy[67]	RCT	29			•	•			•		•
Laser vs. photodynamic therapy	Jimenez-1999, Spain[68]	RCT	31			•	•					•
Laser vs. Electrocautery	van Boxem-1999, Netherlands[69]	NRC	31			•	•			•		•
	Overall	6	342	0	0	6	5	0	0	5	2	6

BCHY: brachytherapy; DSS: disease specific survival; EBRT: external beam radiotherapy; FQ: fair quality; GQ: good quality; KQ: key question; LCT: local control; N: total sample size of the study; NRC: nonrandomized comparative study; OS: overall survival; PQ: poor quality; QOL: quality of life; RCT: randomized controlled trial; SC: symptom control; TOX: toxicity

Key Points

- All RCTs included in this Report were poor quality according to the USPSTF rating criteria. Further analysis of this is provided in the Discussion section that follows.
- Evidence from 6 comparative studies is insufficient to draw conclusions about relative benefits and harms of 6 unique treatment comparisons (brachytherapy plus EBRT versus brachytherapy alone; brachytherapy plus EBRT versus EBRT alone; brachytherapy versus EBRT; laser plus brachytherapy versus laser alone; laser versus electrocautery or photodynamic therapy) for local therapies in symptomatic inoperable patients with obstructive endoluminal NSCLC.
- The evidence comprises direct outcomes (OS), symptom relief and treatment-related toxicities.
- Overall, treatment-related toxicities varied according to type of intervention. Hemoptysis was the most common toxicity reported across studies. There may be under-reporting 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.

Table 10. Study characteristics of comparative studies

Treatment	Study	N	Stage Distribution	Histopathology Confirmation	Age, years[Ψ]	Females	PS
BCHY + EBRT vs. BCHY alone	Mallick-2006, India[64] (RCT)	N: 45 (100%) EBRT+BCHY-16Gy: 15 (33.3%) EBRT+BCHY-10Gy: 15 (33.3%) BCHY-15Gy: 15 (33.4%)	III: 45 (100%)	Yes	64.5 (35-75)	Total: 2 (4%)	NR
BCHY + EBRT vs. EBRT alone	Langendjik-2001, Netherlands[65] (RCT)	N: 95 (100%) EBRT+BCHY: 47 (49%) EBRT: 48 (51%)	EBRT +BCHY vs. EBRT I: 4 (9%) vs. 5 (10%) III: 43 (91%) vs. 43 (90%)	Yes	EBRT+BCHY: 67 (±9) EBRT: 68 (±9)	EBRT+BCHY: 9 (19%) EBRT: 8 (17%)	NR
BCHY vs. EBRT	Stout-2000, UK[66] (RCT)	N: 108 (100%) BCHY: 49 (49%) EBRT: 50 (51%)	NR	Yes	68[A] (40-84)	20 (20%)	NR
Laser + BCHY vs. laser alone	Chella-2000, Italy[67] (RCT)	N: 29 (100%) YAGL+BCHY: 14 (48%) YAGL: 15 (52%)	NR	Yes	61[A] (47-76)	6 (21%)	WHO 0: 3 (10%) I: 11 (40%) II: 15 (52%)
Laser vs. PHDT	Jimenez-1999, Spain[68] (RCT)	N: 31 (100%) PHDT: 14 (45%) YAGL: 17 (55%)	PHDT vs. YAGL I: 3 (21%) vs. 1 (6%) II: 1 (7%) vs. 0 III: 5 (36%) vs. 11 (65%) IV: 4 (24%) vs. 3 (21%) R: 2 (14%) vs. 1 (6%)	Yes	64 (±7)	0	NR
Laser vs. ECAU	van Boxem-1999, Netherlands[69] (NRC)	N: 31 (100%) YAGL: 14 (45%) ECAU: 17 (55%)	YAGL vs. ECAU IV: 6 (43%) vs. 6 (35%) IIIB: 6(43%) vs. 10 (59%) IIIA: 2 (14%) vs. 1 (6%)	Yes	YAGL : 61 (37-88) ECAU: 62 (47-79)	N: 10 (32%) YAGL: 3 (21%) ECAU: 7(41%)	NR

BCHY: brachytherapy; EBRT: external beam radiotherapy; ECAU: electrocautery; Gy: gray; N: total sample size of the study; NR: not reported; NRC: nonrandomized comparative study; PHDT: photodynamic therapy; PS: Performance status; R: Recurrent; RCT: randomized controlled trial; WHO: World Health Organization; YAGL: yttrium aluminum garnet laser

[Ψ] Values are mean (±SD) or median (range) unless specified, [A] Mean (range)

Description of Comparative Studies According To Intervention(s)

Brachytherapy Plus EBRT versus Brachytherapy Alone

One RCT[64] compared brachytherapy plus EBRT versus brachytherapy alone and included a total of 45 patients. These 45 patients were randomized equally across three treatment groups; EBRT plus brachytherapy (16Gy), EBRT plus brachytherapy (10Gy) and brachytherapy (15Gy) alone. All patients in the first two treatment arms received the same dose of EBRT (30 Gy in 10 fractions over 2 weeks). The authors assessed treatment harms at a predefined time periods (at weekly intervals for acute toxicities) using a standardized Radiation Therapy Oncology Group morbidity scoring criterion, which was the strength of the study. Weaknesses of the study included lack of sample size calculation, small number per treatment group, and lack of defined statistical adjustments for multiple statistical comparisons. These weaknesses impacted the USPSTF domain of "appropriate analysis of results." Further no details were provided on randomization or allocation concealment, which adversely affected the USPSTF domain of "assembled comparable groups." Therefore, we judged this study to have a poor USPSTF quality rating.

The response rate of dyspnea, cough, hemoptysis and obstructive pneumonia among the 3 treatment groups was similar between groups and there was not statistically significant difference between any treatment arms. The authors did not provide clear definitions of what constituted a partial or complete response for obstructive symptoms. Though the authors reported significant improvement in obstruction scores as well as multiple QOL scores (including sub-domains) within treatment groups, they did not report the results of between treatment groups. Survival data was not reported. Using the RTOG morbidity scoring criteria, the authors did not observe any grade II-grade IV acute toxicities. One patient died due to hemoptysis in the treatment group that received brachytherapy alone.

Table 11. Comparative effect of brachytherapy plus EBRT versus brachytherapy alone on obstructive symptoms in the Mallick study[64]

Treatment groups	Time	Dyspnea n(%)	Cough n(%)	Hemoptysis n(%)	Obstructive pneumonia n(%)
EBRT+BCHY-16Gy (n=15)	Baseline	15 (100)	15 (100)	9 (60)	9 (60)
	Post Rx*	14 (93)	12 (80))	9 (100)	9 (100)
EBRT+BCHY-10Gy (n=15)	Baseline	13 (87)	15 (100)	13 (87)	10 (67)
	Post Rx*	12 (92)	13 (87)	13 (100)	7 (70)
BCHY-15Gy (n=15)	Baseline	15 (100)	15 (100)	12 (80)	10 (67)
	Post Rx*	13 (87)	13 (87)	10 (82)	8 (80)

BCHY: brachytherapy; EBRT: external beam radiotherapy; Gy: gray; n: number
*Represents number of patient who had complete or partial response.
Note: There was not statistically significant difference between any treatment arms.

Table 12. Comparative effect of brachytherapy plus EBRT versus brachytherapy alone on quality of life outcomes in the Mallick study[64]

Treatment groups	Time	QLQ-C3 (Global Health status)	QLQ-C3 (Physical Functioning):
EBRT+BCHY-16Gy (n=15)	Baseline	37	71
	Post Rx	75 (↑103%)	90 (↑27%)
EBRT+BCHY-10Gy (n=15)	Baseline	35	74
	Post Rx	63 (↑80%)	85 (↑15%)
BCHY-15Gy (n=15)	Baseline	34	56
	Post Rx	62 (↑82%)	78 (↑39%)

BCHY: brachytherapy; EBRT: external beam radiotherapy; Gy: gray; n: number; QLQ-C3: quality of life questionnaire; QOL: quality of life; Rx: treatment

Table 13. USPSTF study quality ratings of the Mallick study[64]

Assembled CG	Maintained CG	Minimal LTFU	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
No	Yes	Yes	No	Yes	Yes	No	Poor

CG: comparable groups; LTFU: loss to followup; USPSTF = U.S. Preventive Services Task Force

Brachytherapy Plus EBRT versus EBRT Alone

One RCT[65] compared brachytherapy plus EBRT versus EBRT alone. The study was planned to recruit a total of 160 patients with an 80 percent power to detect a 25 percent decrease in the rate of palliation of dyspnea with 0.05 type-I error. However, the study was discontinued prematurely due to lack of patient accrual. The authors reported results of 95 evaluable patients who were randomized to brachytherapy plus EBRT (n=47) or EBRT alone (n=48) using a central randomization process. We rated the USPSTF study quality as low. The analysis with only 95 patients was underpowered to detect a prespecified difference in the rate of dyspnea (a primary outcome) and therefore adversely impacted the USPSTF domain of "appropriate analysis of results." The authors did not report the frequency, the process or the method of assessing severity of treatment related toxicity. This negatively impacted the USPSTF domain of "valid measurement."

The results did not show any difference in the response rate of dyspnea in patients treated with EBRT plus brachytherapy versus EBRT alone (46 percent and 37 percent respectively). The median overall survival was similar across both groups; 7.0 (95 percent CI: 5.3 to 8.9) and 8.5 (95 percent CI: 5.4 to 11.6) months respectively. Although the authors assess QOL scores (Dutch version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and lung cancer module QLQ-LC13) both before and after therapy with a 90 percent compliance rate, the results were not reported in the paper and we were unable to find a citation in subsequent years. The proportion of patients with death due to hemoptysis was similar across the two treatment groups (15 percent and 13 percent in the EBRT plus brachytherapy versus EBRT alone group respectively).

Table 14. Comparative effect of brachytherapy plus EBRT versus EBRT alone on obstructive symptoms in the Langendjik study[65]

Treatment groups	Dyspnea	Cough	Hemoptysis	Others
EBRT + BCHY (% response)	18/39 (46%)	24%	86%	Chest pain: 80% Pain in arm/ shoulder: 74%
EBRT (% response)	16/43 (37%) (p=0.29)	38% (NS)	82%	Chest pain: 67% (NS) Pain in arm/ shoulder: 69%

BCHY: brachytherapy; EBRT: external beam radiotherapy; NS: nonsignificant

Table 15. USPSTF study quality ratings of the Langendjik study[65]

Assembled CG	Maintained CG	Minimal LTFU	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
Yes	Yes	Yes	No	Yes	Yes	No	Poor

CG: comparable groups; LTFU: loss to followup; USPSTF = U.S. Preventive Services Task Force

Brachytherapy versus EBRT

One RCT[66] randomized 108 inoperable NSCLC patients with endobronchial tumors to two treatment arms: brachytherapy (n=49) or EBRT (n=50). Nine patients were excluded from the analysis. The primary aim of the study was to evaluate symptom relief, treatment-related toxicities and impact on quality of life (QOL). The strength of the study was that it assessed treatment harms adequately at a pre-defined time periods using patient questionnaires but did not use a standardized scoring criteria to rate severity of treatment-related toxicities. The study was judged to have a poor quality on USPSTF rating for failing to appropriately take into account potential confounding—here fundamentally important for estimating an unbiased effect estimated owing to its time-dependent nature). Fifty-one percent in the brachytherapy arm received EBRT if the symptoms persisted or deteriorated or if the symptoms recurred. Similarly 28 percent in the EBRT arm received brachytherapy. In the absence of taking into account this time-dependent confounding (a per protocol analysis with appropriate censoring), it is impossible to judge the magnitude or even direction of potential bias. This fatal flaw in the negatively impacted all three domains of USPSTF quality rating: “maintained comparable groups,” “measurements valid” and “appropriate analysis of results.” Further, lack of details about randomization and allocation concealment adversely impacted the domain of “assembled comparable groups.”

The response to treatment measured as positive symptom (improvement or no change in symptom severity from baseline to 4 and 8 weeks after treatment) by the physician was similar across two treatment arms. Though survival was not a planned endpoint, the EBRT treatment arm had a statistically significant higher survival than the brachytherapy arm (287 versus 250 days at 1 year, p=0.04). The authors did not report the treatment related toxicities in detail except that they were similar across two treatment groups. Four (8 percent) and three (6 percent) patients died due to hemoptysis in the brachytherapy and EBRT group, respectively.

Table 16. Comparative effect of brachytherapy versus EBRT on obstructive symptoms in the Stout study[66]

Rx groups	Time	Dyspnea	Hemoptysis	Breathlessness
BCHY (% of positive symptom endpoints)	4 weeks	59% (n=41)	85% (n=41)	78% (n=41)
	8 weeks	50% (n=46)	78% (n=46)	59% (n=46)
EBRT (% of positive symptom endpoints)	4 weeks	59% (n=29)	90% (n=29)	66% (n=29)
	8 weeks	67% (n=46)	89% (n=46)	78% (n=46)

BCHY: brachytherapy; EBRT: external beam radiotherapy; n: number
Note: There was not statistically significant difference between any treatment arms.

Table 17. USPSTF study quality ratings of the Stout study[66]

Assembled CG	Maintained CG	Minimal LTFU	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
No	No	Yes	No	Yes	Yes	No	Poor

CG: comparable groups; LTFU: loss to followup; USPSTF = U.S. Preventive Services Task Force

EBRT versus Endobronchial Treatments (Brachytherapy, Laser or Cryotherapy)

One RCT[75] randomized patients to EBRT or endobronchial treatment (clinician choice of any one endobronchial treatment -brachytherapy, laser-therapy or cryotherapy). This study was designed to have a 90 percent power to detect a difference of 15 percent in the relief of breathlessness at 0.05 significance level with 400 patients randomized across 4 treatment arms. The trial[75] was discontinued before completion due to lack of patient accrual. The authors presented data for only 75 patients, of whom 16 patients did not receive the allocated treatment. As a result, the interpretation of available data for 59 patients distributed across four treatment arms poses significant limitations, namely small number per group and uncertainty about the preservation of randomization sequence. Further, the data for three different endobronchial treatment groups is reported cumulatively which does not allow comparison of treatment effects. Therefore, we did not report the data for this study in this report. Details of this study are provided in the abstraction tables in Appendix C.

Laser plus Brachytherapy versus Laser Alone

There is one RCT[67] that compares combination treatment of laser plus brachytherapy versus laser therapy only. This study by Chella el al.,[67] randomized 29 patients across two treatment arms: laser plus brachytherapy (n=14) versus laser (n=15) alone. This small study lacked details on randomization & allocation concealment. It did not report the NSCLC staging of patients, which is an important prognostic factor. These factors adversely affected the USPSTF domain of "assembled comparable groups." The authors did not report the frequency, the process or the method of assessing severity of treatment related toxicity. This negatively impacted the USPSTF domain of "measurements valid." We therefore rated this study to have a poor USPSTF quality rating.

The reported median overall survival in the two treatment groups was not statistically significant different between the two treatment group (10.3 months and 7.4 months respectively). Speiser's index (a semi-quantitative score where a higher score indicates severe obstruction)

reduced by 4.2 and 3.4 points in the combined versus single treatment group respectively. This reduction in score was not statistically different between the two groups. The authors also reported the pretreatment and post-treatment values of lung function tests but there were no statistically significant differences between the treatment groups. One patient died due to hemoptysis 12 months after treatment in the laser plus brachytherapy group.

Table 18. Comparative effect of laser plus brachytherapy versus laser alone on obstructive symptoms in the Chella study[67]

Treatment groups	Speiser's index
Laser + brachytherapy	Pre: 6.9 (±0.7) Post: 2.7 (±0.9)
Laser alone	Pre: 6.4 (±0.7) Post: 3.0 (±0.8)

N: total sample size of the study; Rx: treatment

Table 19. USPSTF Study quality ratings of the Chella study[67]

Assembled CG	Maintained CG	Minimal LTFU	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
No	Yes	Yes	No	Yes	Yes	Yes	Poor

CG: comparable groups; LTFU: loss to followup; USPSTF = U.S. Preventive Services Task Force

Laser versus Photodynamic Therapy

One RCT[68] randomized 31 NSCLC patients with airway obstruction to either photodynamic therapy (n=14) versus laser therapy (n=17). The study assessed treatment harms at a pre-defined and regular time periods and assessed causality but the authors did not report using a standardized criteria to assess the severity of treatment-related toxicities. This was a small study that lacked details on randomization and allocation concealment. At the baseline, the proportion of patients with stage III-IV cancer in the photodynamic group and laser group was 57% (8 of 14) and 88% (15 of 17) respectively. The authors did not explain the imbalance in tumor stage distribution even though it was a randomized study. Further, the authors did not report whether they adjusted for the baseline differences in the outcomes. These factors negatively affected the USPSTF domain of "assembled comparable groups." We therefore judged this study to have a poor USPSTF quality rating.

Median survival was reported to be longer in the photodynamic versus laser group (265 versus 95 days, p=0.007). Though quantitative symptom relief was not reported, the authors described amelioration of symptoms to be similar in both treatment groups. Two patients (one in each group) died from hemoptysis while there was one probable death due to treatment in the photodynamic therapy-treated group.

Table 20. USPSTF Study quality ratings of the Jimenez study[68]

Assembled CG	Maintained CG	Minimal LTFU	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
No	Yes	Yes	Yes	Yes	Yes	No	Poor

CG: comparable groups; LTFU: loss to followup; USPSTF = U.S. Preventive Services Task Force

Laser versus Electrocautery

One nonrandomized retrospective study[69] conducted with 29 patients compared the effects of treatment with laser (n=14) versus electrocautery (n=17) on dyspnea relief in NSCLC patients with tracheobronchial obstruction due to an endobronchial tumor. The study was judged to have poor quality on USPSTF quality rating because of lack of adjustment for any potential confounders given that it was a nonrandomized retrospective study with imbalanced distribution of prognostic factors at the baseline. A disproportionate number of patients had received previous treatment in the laser treated group (93 percent) as compared with the electrocautery group (53 percent). Further, the mean time from diagnosis to study treatment was different in the two groups (4.7 versus 7.5 months in laser versus electrocautery group). These factors negatively affected the USPSTF domain of "assembled comparable groups."

The reported mean survival and percent improvement of symptoms was similar in both groups. The mean survival was 8.0±2.5 and 11.5±3.5 months in the laser and electrocautery treated groups respectively. The proportion of patients with symptom improvement (rated on a dichotomous scale by the treating clinician) was 10 (71 percent) and 13 (76 percent) in the laser and electrocautery treated groups respectively.

Table 21. USPSTF Study quality ratings of the Boxem study[69]

Assembled CG	Maintained CG	Minimal LTFU	Measurements equal, valid, and reliable	Interventions clearly defined	Important outcomes considered	Appropriate analysis of results	Overall USPSTF rating
No	Unclear	Yes	No	Yes	Yes	No	Poor

CG: comparable groups; LTFU: loss to followup; USPSTF = U.S. Preventive Services Task Force

Study Characteristics of Noncomparative Studies

There were a total of 11 noncomparative studies[94-104] that included 858 patients given 8 distinct treatment modalities (3 single intervention: brachytherapy, photodynamic therapy, radio frequency ablation; 5 multiple interventions: brachytherapy plus EBRT, brachytherapy plus photodynamic therapy plus chemotherapy, EBRT plus chemotherapy, stenting plus brachytherapy and stenting plus laser therapy). Among these 11 noncomparative studies, data for 3 studies[99, 101, 104] were extracted for a single arm from an otherwise comparative study. Three studies (27 percent) originated in the United States, seven were from Europe (64 percent), and one (9 percent) was from former Yugoslavia.

Table 22. Overview of noncomparative studies of local endobronchial therapies

Treatment	Author, Year	Time	N	OS	DSS	LCT	SC	QOL	TOX
BCHY	Celebioglu-2002, Turkey[95]	R	95				•		•
BCHY	Guilcher-2011, France[97]	R	226	•	•	•			•
BCHY	Petera-2001, Czech Republic[101] C	NR	41	•			•		
PHDT	Jones-2001, USA[98]	R	10	•					
RFA	Lencioni-2008, Multiple Countries[99] C	P	33	•	•			•	•
BCHY + EBRT	Muto-2000, Italy[100]	P	320	•			•		
BCHY + EBRT	Vucicevic-1999, Yugoslavia[102]	R	39	•			•		•
BCHY + STNT	Allison-2004, USA[94]	P	10	•		•		•	
LASR + STNT	Chhajed-2006, Switzerland[104] C	R	52						•

Treatment	Author, Year	Time	N	OS	DSS	LCT	SC	QOL	TOX
EBRT + CHEM	Celikoglu-2006, Turkey[96]	P	23				•		
BCHY + CHEM + PHDT	Weinberg-2010, USA[103]	NR	9	•					•

DSS: disease specific survival; LCT: local control; N: total sample size of the study; NSCLC: non-small cell lung cancer; OS: overall survival; QOL: quality of life; RCT: randomized controlled trial; SAS: single-arm study; SC: symptom control; TOX: toxicity

We did not use the data from these 11 noncomparative studies for assessing strength of evidence regarding the benefits (symptom relief, survival, QOL) of local endobronchial interventions. As per AHRQ guidance on comparing harms about medical interventions,[105] data about harms from observational studies should always be assessed. This is because quantity and quality of harms reporting in clinical trials is frequently inadequate and hypotheses are usually designed to evaluate benefits than harms. Further, clinical trials usually are not large enough to capture rare adverse events nor are they long enough to capture late adverse events. Moreover, clinical trials tend to include homogenous and healthier subjects who are less likely to have adverse events than the general population.[105] Therefore, we report the treatment-related toxicities data from these 11 noncomparative studies. These data are compiled in Table 23.

Table 23 shows treatment-related toxicities reported in at least 2 percent of the study population. In the largest prospective study[100] of 320 patients who were treated with a combination of brachyherapy and EBRT, radiation bronchitis was the most common treatment-related toxictiy observed. The incidence of grade 2, 3 and 4 radiation bronchitis was 7, 10 and 8 percent respectively. In the second largest single arm study by Guilcher,[97] 226 patients with endobronchial NSCLC treated with brachyhrepay alone were analysed retrospectively. The incidence of radiation bronchitis was 12 percent. Six percent (n=13) of patients died due to complication (10 hemoptysis, 2 of necrosis and 1 of radiation stenosis). The authors of the study did not specify if these were treatment related ccomplications or not. There was only one study[99] that reported incidence of pneumothorax with use of RFA. Pneumothorax occurred in 13 percent of patients included in the study. The incidence of hemoptysis in more than 2 percent of study subjects was observed in 4 studies[97, 100, 102, 104] and ranged from 2 to 7 percent. The toxicity reporting criteria for each study (when provided by the authors) are shown in Appendix C.

Table 23. Treatment-related toxicities in noncomparative studies

Rx	Study	Hemoptysis	Pneumothorax	Radiation bronchitis	Death	Others
BCHY	Muto-2000 (N=320)[100]	10 (4%)	-	Grade 2: 20 (7%) Grade 3: 28 (10%) Grade 4: 23 (8%)	-	Broncho esophageal fistulas: 3 (1%)
BCHY	Celebioglu-2002 (N=95)[95]		0	-		Fistula: 0 Cardiovascular problems: 0
BCHY	Guilcher-2011 (N=226)[97]	15 (7%)	3 (1%)	Grade II: 28 (12%)	Death due to complication: 13 (6%)	Bronchial stenosis: 21 (9%) Necrosis of bronchial wall: 7 (3%) Grade 2 mucitis: 9 (4%)
RFA	Lencioni-2008 (N=33)[99]	-	5 (13%)[Ψ]	-	-	
BCHY + EBRT	Vucicevic-1999 (N=39)[102]	1/30 (3%)	-	-	-	Esophagitis: 3/39 (8%) Cardiac arrhythmia: 1/39 (3%) Pulmonary fibrosis: 4/39 (10%) Esophageal stricture: 1/39 (3%) Fistulae: 1/39 (3%)
STNT + LASR	Chhajed-2006 (N=52)[104]	1 (2%)	-	-	Death within 24 h of the procedure: 1 (2%)	Stent migration: 3 (6%) Mucous plugging of the airway stent: 2 (4%)
BCHY + CHEM + PHDT	Weinberg-2010 (N=9)[103]	-	-	-	-	Bronchial contraction: 5/9 (56%) Occlusion from bronchial contraction: 2/9 (22%) Photosensitivity: 2/9 (22%)

BCHY: brachytherapy; CHEM: chemotherapy; EBRT: external beam radiotherapy; HDR: high-dose rate; N: total sample size of the study; NR: not reported; NRC: nonrandomized comparative study; PHDT: photodynamic therapy; RFA: radiofrequency ablation; STNT: stenting

[Ψ] This is procedure level and not patient data. Forty procedures were done in 33 patients and 5 procedures were associated with pneumothorax.

Discussion

Overview

This chapter presents a discussion of the results of the comparative effectiveness review (CER) organized with Key Questions (KQs) 1, 2 and 3 following in order. It is organized as follows:

- Key findings
- Strength of evidence
- Relationship of the findings to existing information
- Applicability of the findings
- Implications for clinical and policy decisions
- Limitations of the CER process as it pertains to this CER
- Limitations of the evidence base
- Research gaps and conclusions

Key Findings

Key Question 1: Local Interventions in Medically Inoperable Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)

- Thirty-three single-arm studies reported clinical benefits and harms associated with the use of three-dimensional radiotherapy (3DRT), proton beam radiotherapy (PBRT), radiofrequency ablation (RFA) and stereotactic body radiotherapy (SBRT) to treat patients with stage I NSCLC who were deemed to be medically inoperable. Clinical benefits included post-treatment overall survival (OS), cancer-specific survival (CSS) and local control (LCT) rates. Harms were radiation-induced for 3DRT, PBRT and SBRT and procedural complications for RFA.
- There were no studies that directly compared the relative benefits or harms of the interventions of interest in inoperable stage I NSCLC patients.
- The evidence is insufficient to answer Key Question 1.

Key Question 2: Local Interventions in Medically Operable Patients with Stage I NSCLC

- Four single-arm studies reported clinical benefits and harms associated with the use of PBRT and SBRT to treat patients with stage I NSCLC who were deemed to be medically operable. Clinical benefits included post-treatment OS, CSS and LCT rates. Harms were radiation-induced for PBRT and SBRT.
- There were no studies that directly compared the relative benefits or harms of the interventions of interest in medically operable stage I NSCLC patients.
- The evidence is insufficient to answer Key Question 2.

Key Question 3: Local Interventions for Inoperable Patients with NSCLC and Symptoms due to an Endoluminal Lesion

- Six comparative studies reported clinical benefits and harms associated with the use of local therapies (EBRT, brachytherapy, laser therapy, photodynamic therapy and electrocautery) for palliation in symptomatic inoperable patients with obstructive endoluminal NSCLC. Reported clinical benefits included post-treatment symptom relief and OS. Harms were hemoptysis, pneumothorax, radiation bronchitis, bronchoesophageal fistulas and photosensitivity.
- One comparative study was available per treatment comparison. All six comparative studies were of poor quality and therefore the evidence from these studies had a high risk of bias, consistency was unknown, evidence was direct and all were imprecise.
- The evidence is insufficient to answer Key Question 3.

Strength of Evidence

To evaluate the strength of the body of evidence, we used the EPC approach developed for the Evidence-based Practice Center (EPC) program and referenced in the *Methods Guide* which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group[30, 35] This system explicitly addresses four required domains: risk of bias, consistency, directness, and precision.

Key Question 1

As shown in Table 24 below, the overall strength of evidence 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.

Thirty-three single-arm studies were available. Direct outcomes of interest were OS, CSS, and toxicities. The risk of bias was high. The consistency of effect size direction cannot be determined in the absence of comparative studies. No direct comparative evidence is available among interventions. Precision cannot be determined in the absence of direct comparative evidence among interventions.

Table 24. Strength of evidence for local interventions in medically inoperable stage I NSCLC patients

Evidence Base	Risk of bias	Consistency	Directness	Precision	Overall Strength of Evidence
33 single-arm studies reported clinical outcomes associated with the use of 3DRT (7 studies,[50, 51, 54, 55, 75-77] total n = 240 patients), PBRT (3 studies,[36-38] total n = 144 patients), RFA (1 study,[39] n = 19 patients), and SBRT (22 studies,[40-61] total n = 1413 patients).	*High*	*Unknown*	*Direct*	*Imprecise*	*Insufficient*

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

Key Question 2

As shown in Table 25, the overall strength of evidence is insufficient to form conclusions about the comparative benefical effects or toxicities of PBRT or SBRT in the treatment of stage I NSCLC in medically operable patients.

Four single-arm studies were available.[37, 56, 62, 63] Direct outcomes of interest were OS, CSS, and toxicities. The risk of bias was high. The consistency of effect size direction cannot be determined in the absence of comparative studies. No direct comparative evidence is available among interventions. Precision cannot be determined in the absence of direct comparative evidence among interventions.

Table 25. Strength of evidence for local interventions in medically operable stage I NSCLC patients

Treatment and Evidence Base	Risk of bias	Consistency	Directness	Precision	Overall Strength of Evidence
Four single-arm studies reported clinical outcomes associated with the use of SBRT (3 studies, [56, 62, 63] n = 278) or PBRT (1 study,[37] n = 28)	*High*	*Unknown*	*Direct*	*Imprecise*	*Insufficient*

n: number; NSCLC: non-small cell lung cancer; PBRT: proton beam radiotherapy; SBRT: stereotactic body radiotherapy

Key Question 3

Overall, evidence is insufficient to form conclusions about the benefits (symptom relief, survival) and harms (treatment related toxicities) of local therapies (brachytherapy plus EBRT versus brachytherapy alone; brachytherapy plus EBRT versus EBRT alone; brachytherapy versus EBRT; laser plus brachytherapy versus laser alone; laser versus electrocautery or photodynamic therapy) in symptomatic inoperable patients with obstructive endoluminal NSCLC.

Strength of Evidence

Brachytherapy plus EBRT versus Brachytherapy Alone

The evidence for this comparison comprised one small RCT[64] (n=45, 15 patients per treatment arm). This study is considered to have a high risk of bias because the study 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 evidence for symptom relief, survival and treatment related toxicities is imprecise. Therefore, the SOE for brachytherapy plus EBRT versus brachytherapy alone was insufficient.

Brachytherapy plus EBRT versus EBRT alone

The evidence for this comparison comprised one small RCT[65] (n=95). This study was considered to have a high risk of bias primarily because the study was discontinued prematurely due to lack of patient accrual. This was considered a fatal flaw. The consistency of the evidence was unknown as it was a single RCT without confirmation from any other study. The evidence for symptom relief, survival and treatment related toxicities is imprecise. Therefore, the SOE for brachytherapy plus EBRT versus EBRT alone was insufficient.

Brachytherapy versus EBRT

The evidence for this comparison comprised one small RCT[66] (n=99). This study is considered to have a high risk of bias because the study failed to adjust for potential confounding secondary to cross-over of a large proportion of patients between treatment arms during the study period. This was considered a fatal flaw. The consistency of the evidence was unknown as it was a single RCT without confirmation from any other study. The evidence for symptom relief and treatment related toxicities is imprecise. The evidence for survival was precise. Therefore, the SOE for brachytherapy versus EBRT alone was insufficient.

Laser plus Brachytherapy versus Laser Alone

The evidence for this comparison comprised one small RCT[67] (n=29). This study is 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 evidence for symptom relief, survival and treatment related toxicities is imprecise. Therefore, the SOE for laser plus brachytherapy versus laser alone was insufficient.

Laser versus Photodynamic Therapy

The evidence for this comparison comprised one small RCT[68] (n=31). This study was considered to have a high risk of bias primarily because the treatment arms had serious imbalances at the baseline. The proportion of patients with stage III-IV cancer was much smaller in the photodynamic group (57%, 8 of 14) than the laser group (88%, 15 of 17). This was considered a fatal flaw. The consistency of the evidence was unknown as it was a single RCT without confirmation from any other study. The evidence for treatment related toxicities is imprecise. The evidence for survival was precise. Therefore, the SOE for brachytherapy versus EBRT alone was insufficient.

Laser versus Electrocautery

The evidence for this comparison comprised one small non-randomized comparative study[69] (n=29). This study is considered to have a high 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 percent) as compared with the electrocautery group (53 percent). Further, the mean time from diagnosis to study treatment was different in the two groups (4.7 versus 7.5 months in laser versus electrocautery group). The consistency of the evidence was unknown as it was a single RCT without confirmation from any other study. The evidence for symptom relief and survival is imprecise. Therefore, the SOE for laser versus electrocautery was insufficient.

Table 26. Strength of evidence for local therapies for symptoms secondary to an inoperable obstructive endoluminal NSCLC

Treatment and evidence base	Outcome	Unit of Measure	Risk of bias	Consistency	Directness	Precision	SOE
Brachytherapy plus EBRT versus brachytherapy alone (1 RCT, n=45)[64]	Symptom relief	Incidence and response rate	High	Unknown	Yes	Imprecise	*Insufficient*
	QOL	EORTC QLQ-C30 & LC 13 V3.0					

Treatment and evidence base	Outcome	Unit of Measure	Risk of bias	Consistency	Directness	Precision	SOE
	Treatment toxicity	Incidence of Grade ≥II RTOG morbidity scoring scriteria					
Brachytherapy plus EBRT versus EBRT alone (1 RCT, n=95)[65]	Symptom relief	Response rate	High	Unknown	Yes	Imprecise	*Insufficient*
	Survival	Overall survival					
	Treatment toxicity	Incidence					
Brachytherapy versus EBRT (1 RCT, n=99)[66]	Symptom relief	% improvement	High	Unknown	Yes	Imprecise	*Insufficient*
	Survival	Overall survival	High	Unknown	Yes	Precise	*Insufficient*
	Treatment toxicity	Incidence	High	Unknown	Yes	Imprecise	*Insufficient*
Nd-YAG plus Brachytherapy versus Nd-YAG alone (1 RCT, n=29)[67]	Symptom relief	Speiser's index	High	Unknown	Yes	Imprecise	*Insufficient*
	Survival	Overall survival					
	Treatment toxicity	Incidence					
Photodynamic Therapy versus Laser (1 RCT, n= 31)[68]	Survival	Overall survival	High	Unknown	Yes	Precise	*Insufficient*
	Treatment toxicity	Incidence	High	Unknown	Yes	Imprecise	*Insufficient*
Nd-YAG versus Electrocautery (1 NRC, n=29)[69]	Survival	Mean survival	High	Unknown	Yes	Imprecise	*Insufficient*
	Symptom relief	% response					

BCHY: brachytherapy; EBRT: external beam radiotherapy; EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; KQ: key question; n: number; N: total sample size of the study; Nd-YAG: neodymium-doped yttrium aluminum garnet; NSCLC: non-small cell lung cancer; NRC: nonrandomized comparative study; QOL: quality of life; RCT: randomized controlled trial; RTOG: Radiation Therapy Oncology Group; SOE: strength of evidence

Relationship of the findings to existing information

Key Questions 1 and 2

We sought credible sources of evidence-based information on the use of the local interventions assessed in this CER to treat stage I NSCLC. We identified a recent systematic review that examined the effectiveness of SBRT among patients with severe chronic obstructive pulmonary disease (GOLD III-IV).[50] The authors of that review reported limited, noncomparative published data are available to assess outcomes in this setting. An AHRQ Technical Brief reported on the state of the evidence for SBRT in a number of cancers, including NSCLC.[106] The authors of the Technical Brief did not identify any published randomized trials or other comparative studies that compared SBRT to another modality. Our systematic literature search and review did not reveal any relevant evidence-based guidelines we could compare to our findings. Our Report offers the first comprehensive systematic review on this topic.

Key Question 3

This systematic review sought randomized controlled trials that compared local bronchoscopic interventions in patients with an endobronchial NSCLC. We found 5 randomized controlled studies of poor quality and one nonrandomized comparative study that compared 6 unique combinations of bronchoscopic interventions in NSCLC patients. The systematic review

concluded that there is insufficient evidence to conclude relative benefits and harms of one therapy over another for the following six interventions:

- Brachytherapy plus EBRT versus brachytherapy alone
- Brachytherapy plus EBRT versus EBRT alone
- Brachytherapy versus EBRT
- Laser plus brachytherapy versus laser alone
- Laser versus electrocautery
- Laser versus photodynamic

We found one Cochrane systematic review[27] that compares endobronchial brachytherapy with palliative intent for NSCLC patients with other available treatments including EBRT, other bronchoscopic interventions, chemotherapy or best supportive care. The Cochrane review included only RCTs with only metastatic or advanced (stage IIIb and IV) NSCLC patients. The strength of this review is its broader scope as it included all NSCLC stages patients including recurrent patients. Further, we addressed all possible combination of local bronchoscopic therapies and all possible study designs except for case reports. However, unlike the Cochrane review, the present review excluded all studies published prior to 1995 and did not include data from studies that were published as abstracts only.

In concurrence with our findings, the Cochrane review also agreed that the evidence did not provide conclusive results that endobronchial brachytherapy plus EBRT improved symptom relief compared with EBRT alone or there was any conclusive evidence to recommend endobronchial brachytherapy in combination with EBRT, chemotherapy or laser therapy.

The second edition of American College of Chest Physicians (ACCP) Evidence Based Clinical Practice Guidelines[72] for palliative care of lung cancer patients relevant in part to the current context of local bronchoscopic interventions for endoluminal obstruction in NSCLC patients. These guidelines describe the general landscape of palliative bronchoscopic therapies including mechanical debridement, laser, argon plasma coagulation, brachytherapy, cryotherapy, balloon dilatation, photodynamic therapy, electrocautery and stenting. The ACCP guidelines[72] state that all such interventions provide significant relief from dyspnea and hemoptysis in majority of patients but do not discuss comparative effectiveness (harms and benefits) of these therapies. The guideline recommends treatment with appropriate therapies (Grade 1C) for all lung cancer patients who complain of dyspnea with a potentially correctable cause. These guidelines also state that in all lung cancer patients with large volume hemoptysis, bronchoscopic evaluation of source of bleeding followed by endobronchial management options such as argon plasma coagulation, laser and electrocautery is recommended (Grade 1C).

Applicability Of The Findings

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 therapies for stage I NSCLC. The evidence for KQ 1 and 2 does not reach that level, so we have primarily limited comments to relevance of the PICOTS (population, intervention, comparator, outcomes, timing, setting) elements.[85] The PICOTS format comprises a practical and useful structure to review applicability in a systematic manner and is employed as follows, minus the timing element.

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 are selected for a particular treatment by their clinician rather than through random allocation. The reasons why a patient may be chosen for a particular therapy will vary by clinician preferences, center resources, patient characteristics, and preference. This evidence base is therefore insufficient to support any attempt to draw comparative conclusions.

Table 27. Summary of applicability of evidence for Key Questions 1 and 2

Domain	Applicability of Evidence
Populations	• Overall the patients in the single-arm studies included were not suitable for surgery, or suitable for surgery but declined it. • The patients with stage I NSCLC in the studies included in this report appear representative of cases that would be considered for a local intervention. • Patients typically were in their late 60s to mid-70s, congruent with the incidence of stage I NSCLC that 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 than the inoperable population of KQ1. Compared with the latter, however, they represent a somewhat healthier group, albeit perhaps not compared with the population that undergoes surgery.
Interventions	• 3DRT, IMRT and SBRT represent a progression of technological advances in the delivery of conformal photon radiotherapy. The major benefit of each relative to traditional wide-field 2DRT is the ability to deliver tightly focused cytotoxic radiation to a tumor volume that is precisely delineated using a CT-based planning system. • 3DRT represents a minimum technical capability for delivery of conformal radiotherapy, and is widely available. • IMRT is not as widely available as 3DRT, and requires a higher level of planning and quality assurance. • The institutional programmatic requirements for SBRT are similar to those of IMRT. • SBRT is not as widely available as 3DRT or IMRT, but our literature review suggests there has been growing interest in this technology in this setting, to the point that is may supplant the older technologies in the KQ1 and KQ2 settings. • This CER did not allow for a rigorous and systematic comparison of the relative performance of local therapies stratified by technological factors. How these factors may alter health outcomes remains unclear. • The applicability of the evidence for PBRT and RFA is unknown due to limited evidence.
Comparators	• See above for Intervention
Outcomes	• The major health outcomes in this CER are OS, CSS, and LCT, typically reported over a period of one to five years. • OS is the gold standard direct outcome for any cancer intervention study. • CSS reflects the true effect of a cancer intervention on the disease. It 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 still 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 around systemic chemotherapy. This is a potentially perilous position for the medically frail patients considered in KQ1, and perhaps many of those in KQ2.
Setting	• The evidence for KQ 1 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 on-going 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; n: number; LCT: local control; NSCLC: non-small cell lung cancer; OS: overall survival; PBRT: proton beam radiotherapy; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy

Key Question 3

Table 28. Summary of applicability of evidence for Key Question 3

Domain	Applicability of Evidence
Populations	• The patients in the studies included in this report appear 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 61-68 years and this is congruent with the incidence of NSCLC that tends to rise with age.
Interventions	• The 5 single modality interventions (brachytherapy, EBRT, electrocautery, laser, photodynamic) and 2 dual modality interventions (laser plus brachytherapy and brachytherapy plus EBRT) represent a general landscape of current treatments options for patients with endoluminal obstructive NSCLC and therefore are applicable.
Comparators	• See above for Intervention
Outcomes	• The major outcomes of interest were symptom relief, overall survival, disease specific survival, quality of life and treatment-related toxicity. • Though OS is the gold standard direct outcome for any cancer intervention study, it may not be the best measure of efficacy of a palliative intervention in symptomatic patients. Immediate relief of obstructive symptom and improvement in quality of life 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 Outcomes Measures),[71] both generic and disease specific instruments exists 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 EORTC QLQ-C30, EORTC QLQ-LC13 and FACT-L. However, QOL data was reported only by one small study of the six comparative studies. Therefore, applicability of the current evidence base on QOL cannot be determined.
Setting	• 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 as part of our systematic review.

EBRT: external beam radiotherapy; EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D: self-report questionnaire; NSCLC: non-small cell lung cancer; QOL: quality of life; SF-36: Short Form 36 Health Survey

There were multiple shortcomings with the current evidence base that precludes interpretation about general applicability. Firstly, the comparative benefits and harms of various endobronchial treatments are still unknown because of lack of good quality randomized controlled trials. The available studies were all poor quality, often small and not powered to detect a prespecified clinically meaningful difference in a standardized outcome of interest. Secondly, 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. Thirdly, there was a wide variation in the outcomes measures to report symptom relief in the current studies. Fourthly, many studies did not report the frequency, the process or the method of assessing severity of treatment related toxicities and therefore the true harms associated with these interventions are likely to be under-represented in the current data.

Implications for Clinical and Policy Decisionmaking

Our results show there is no direct comparative evidence to support a decision among 3DRT, PBRT, RFA, or SBRT in stage I NSCLC patients. There is a paucity of comparative evidence among any of the interventions considered in KQ3.

In the absence of adequate direct comparative effectiveness data, other factors may be considered in making a treatment decision. Those could include relative convenience, and cost. The latter is outside the scope of this CER. Relative convenience would entail treatment duration and availability or access to a technology. Treatment duration can be substantially different for the interventions considered in KQ 1 and 2. It may reach three weeks or more for 3DRT or IMRT, compared with a week or less for SBRT or RFA. The availability of a technology locally, as opposed to a distant tertiary center, may be very relevant to NSCLC patients who are often elderly and perhaps debilitated by underlying comorbidities. According to the National Association for Proton Therapy (http://www.proton-therapy.org/), PBRT is available for NSCLC therapy at 10 specialized centers in the U.S., with seven under development. Thus, PBRT would be a limited choice for a large proportion of NSCLC patients.

Although we did not formally examine this issue, the body of published literature we identified for this CER suggests interest in SBRT has been growing over the past several years. It may be poised to supplant earlier conformal radiotherapy modalities in treating stage I NSCLC. This view is congruent with results of a recent survey of 1,600 radiation oncologists regarding SBRT use in the U.S.[73, 74] The survey results indicated nearly 64 percent (95 percent CI, 60-68 percent) of radiation oncologists use SBRT in their practice, among whom about 50 percent adopted it in 2008 or later. Among SBRT users in this survey, 89 percent used it to treat lung cancer patients.

From the institutional perspective, decision-makers may face pressures on acquisition that blend considerations of awareness and demand by referring physicians and patients with marketing and competition issues. These may lead to acquisition of one technology over another regardless of the availability of evidence of comparative effectiveness. Clinical uncertainties for all three KQs were a driver of development of this CER. The findings ideally would provide a foundation for critically considering each technology in terms of the evidence available. However, it is unclear whether this will ultimately affect policy decisions.

Limitations of the Comparative Effectiveness Review Process

We expected that the total evidence base would be substantial for this CER. The volume of literature identified in the AHRQ Topic Development and Refinement process suggested the existence of a robust evidence base for all KQs. However, when we began to screen articles, it became evident that there were very few published comparative studies overall, none for KQ1 and KQ2 and only six for KQ3.

Limitations of Evidence Base

The primary limitation of the evidence base is the lack of comparative trials of any design for KQ1 and 2, and a paucity of comparative trials for KQ3. The quality of the single-arm studies for KQ 1 and KQ2 was fair to poor, most often (63 percent) because authors did not report a funding source. Whether this consitutes an important factor to downgrade quality is unclear No other parameter was identified as a consistent factor for downgrading study quality.

Even though comparative studies (five RCTs and one nonrandomized comparative study) were available for KQ3, significant limitations in the quality and quantity of evidence base led us to conclude that the evidence was insufficient to make conclusions about comparative effectiveness of local interventions to treat endobronchial obstructions in NSCLC patients. There was only one study available per six unique treatment comparisons to draw inferences about comparative effectiveness. Therefore the consistency domain for SOE was unknown. All six studies received a low 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 KQ3 did not use statistical adjustment to reduce confounding; such adjustment for confounding should be consistently used in nonrandomized studies.

Research Gaps

Overview

KQ1 considers the relative clinical effectiveness of local interventions—3DRT, SBRT, PBRT and RFA—as sole therapy for patients with stage I NSCLC who are deemed to be medically inoperable. KQ2 addresses the same set of interventions in patients with stage I NSCLC who are deemed operable but who decline resection. The evidence base for KQ 1 and KQ2 comprises single-arm studies. The largest body of evidence is on SBRT, which suggests it may be gaining status among clinicians as a preferred treatment in patients with stage I disease. However, we did not identify evidence that supports one intervention relative to any other. Overall, the strength of the body of evidence is insufficient to draw conclusions on the comparative effectiveness of the interventions in terms of overall survival or cancer-specific survival.

Key Questions 1 and 2

Two international randomized, Phase III clinical trials of surgical resection versus SBRT are recruiting patients (NCT01336894 and NCT 00840749). We identified no ongoing randomized trials that would compare among the interventions or settings addressed in KQ 1 or 2.

The absence of comparative evidence acquired through standardized protocols is the most important research gap we have identified. The two RCTs mentioned above will not reveal relative outcomes among local interventions. There is a need for randomized trials to be performed in the United States population. Assuming a number of impediments (see below) can be surmounted, we see a need for rigorous study as follows:

- Randomized comparative trials of local interventions (e.g., SBRT, 3DRT, IMRT, RFA) in medically inoperable stage I patients, incorporating the following:
    - Standardized patient selection criteria involving thoracic surgeon, medical oncologist, and radiation oncology consultation to assure comparability of patients and minimize bias. Key factors include comorbidity status (particularly cardiopulmonary function and capacity), age, performance status, tumor staging methodology, tumor size and tumor location.
    - Standardized intervention protocols with training and quality assurance programs within and across participating institutions. For radiotherapy, key interventional

factors include the radiotherapy 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, PBRT). RFA factors include power source, power delivered, intralesional temperature achieved, time course of therapy, the type of probe(s) used, and their placement within the lesion.
    - Prespecified followup criteria and methods, in particular notation of subsequent systemic therapy. The latter is a key concern because it is not possible to determine the effect of an intervention administered with systemic therapy.
    - Rigorous, standardized reporting that accounts for all patients and treatments received. Analysis of studies that enroll operable and inoperable patients is possible only if the findings are reported disaggregated. Rigorous methods for conduct of RCTs is urged, particularly intent-to-treat analysis and adjustment of survival data for patients who develop recurrent disease go on to receive systemic therapy. Primary outcomes include overall survival, cancer-specific survival, and local control. Prespecified, systematic collection of adverse events using the latest validated criteria (e.g., NCI CTCAE criteria) is necessary to permit accurate assessment of relative benefits and risks of the interventions.

- Extrapolating results of randomized comparative trial results among inoperable patients that identify the most effective and safe local intervention(s) into medically operable patients who decline surgery, incorporating the following, with key factors, methods, and outcomes listed in the preceding bullet points:
    - Standardized patient selection criteria involving thoracic surgeon, medical oncologist, and radiation oncology consultation to assure comparability of patients and minimize bias.
    - Standardized intervention protocols with training and quality assurance programs within and across participating institutions.
    - Prespecified followup criteria and methods, in particular notation of subsequent systemic therapy.
    - Rigorous, standardized reporting that accounts for all patients and treatments received.

However, a number of general impediments to conducting adequate trials may exist:

- Even though there are no direct comparative trials among the local interventions to suggest one is more effective than another, survey data suggest SBRT is quickly becoming a widely-used modality for stage I NSCLC patients who are medically inoperable or choose to forgo surgical resection.[73, 74]
- In comparison to 3DRT or IMRT, SBRT necessitates fewer treatments, a significant factor that may drive decisions among patients and clinicians.
- Ready access to a specific intervention may be a decision point in clinical practice, in particular considering whether they are available at community-based hospitals or tertiary centers, which could drive patients and their referring physicians toward a specific technology. Nearly 40 percent of solo practitioners in a survey study reported treating patients with SBRT, which suggests this technology is becoming accessible within the broader radiation oncology community.[73, 74]

Key Question 3

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 randomized controlled trials 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 randomized controlled trials 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 toxicities data from various bronchoscopic interventions used for treating endoluminal obstructions from actual clinical practice setting.

While reviewing the published literature we came across two studies that planned a RCT to compare local endobronchial interventions in patients with endobronchial NSCLC but were unable to complete the trial due to lack of patient accrual or never published the trial results. Among these two studies, study by Moghissi et al.,[75] is most notable. The objective of this RCT was to compare two treatment policies in terms of: symptom relief, respiratory function, performance status, quality of life and survival. This study planned to recruit 400 patients in 3 years at 24 clinical centers in the UK. Even though the study organizers had successfully conducted many RCTs in the past, they failed to recruit patient in this clinical setting. Moreover, 20 percent of those randomized did not receive the assigned treatment. Another study by Langendijk[65] that aimed to randomize patients to brachytherapy plus EBRT or EBRT alone arm discontinued their study due to lack of patient accrual before they could complete the planned enrollment of 160 patients.

NSCLC patients with endoluminal obstructions are particularly difficult to randomize in trials because of many issues particularly ethical issues in randomizing critically ill patients. Most of these bronchoscopic interventions are considered complementary and are used sequentially in a clinical setting[76] and therefore randomizing 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 barriers are likely to obviate successful conduct if more RCTs are undertaken in the future.

Thus we propose a prospective cohort study may be able to answer the questions about relative harms and benefits of local endobronchial interventions. Though concerns of selection bias and unknown confounders will always exist in this study design, addressing and collecting data about most relevant confounders a priori can provide much needed informative answers about comparative benefits (including QOL data) and harms of these therapies in population of interest. We recommend that the research team for conducting such a study should be multi-disciplinary including oncologists experienced in treating NSCLC patients with endobronchial obstruction, methodologist with expertise in quality of life measurement, clinical researchers with expertise in planning and conduct of large cohort multicentric studies and ethicists. Relevant outcomes that should be measured in such a study should include symptom control, quality of life, survival and treatment-related adverse effects. Data related to symptom control

should be captured using a standardized validated tool applied uniformly across all interventions. In the current evidence base, Speiser Index was used commonly to assess symptomatic control but the validity and sensitivity of such a tool to capture treatment effect is unknown. Therefore, it is crucial to address and resolve the shortcomings of current tools that are used to symptom control to allow objective and uniform measurements of symptom control. While generic instruments such as SF-36 and EQ-5D have been used in this setting to measure QOL data in such a setting, it is recommended that they are used in conjunction with lung cancer specific measures such as EORTC QLQ-C30, EORTC QLQ-LC13 and FACT-L.

Treatment-related adverse events should be assessed from the date of the procedure extending to a reasonable period of time preferably until death using standardized and well-defined criteria with an independent causality analysis. All such adverse events should be assessed not just by clinicians but the study design should incorporate a process to capture and report adverse event that occur when patients are not under direct medical supervision such as home or long term care facility. Since nonrandomized studies are prone to selection bias, it is crucial to collect data on all potential prognostic covariates in order to adjust for confounding. Such data should include but not 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 data on the operator (expertise, years of experience, size of the facility).

Secondly, we propose setting up a registry to systematically collect treatment- related toxicity data for patients undergoing such procedures. According to the AHRQ publication on registries[107] for evaluating patient outcomes, registries need to be created with a question in mind which will then guide the identification of the target population, the exposures and outcomes of interest, number of patients and length of followup. Registries can be designed as an active surveillance system for identifying harms and may be particularly useful for assessing adverse events.

Conclusion

We conducted a systematic review of the literature to evaluate the comparative effectiveness of local therapies in patients with NSCLC. Our review addressed three Key Questions with three distinct categories of patients: those with stage I NSCLC who were deemed medically inoperable (Key Question 1); those with stage I NSCLC who were deemed medically operable (Key Question 2); and those with symptoms secondary to the presence of endoluminal NSCLC (Key Question 3). For KQ1 and KQ2 we included only single local interventions: 3DRT, PBRT, RFA, and SBRT. For KQ3 we allowed combinations of local therapies including Nd-YAG laser, photodynamic therapy, endobronchial debridement with stenting, and EBRT, as well as systemic chemotherapy.

For all Key Questions, the evidence was insufficient to reach conclusions about the relative effectiveness and safety of the interventions in terms of overall survival, cancer-specific survival, local control, quality of life, symptomatic relief and toxicities.

List of Abbreviations

Abbreviation	Definition
3DRT	Three dimensional radiation therapy
AC	Adenocarcinoma
ACE-27	Adult Co-Morbidity Evaluation-27 scoring system
BAC	Bronchoalveolar carcinoma
BED	Biologically Effective Dose
BI	Bronchus intermedius
BOI	Bronchial abstraction index
CAD	Coronary Artery Disease
CCI	Charlson Comorbidity Index
CGE	Cobalt Gray equivalent
CHF	Congestive Heart Failure
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
CPD	Chronic Pulmonary Disease
CSS	Cancer-specific survival
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular disease
CWP	Chest Wall Pain
DLCO	Diffusion Lung Capacity for Carbon Monoxide
DM	Diabetes mellitus
DSS	Disease-specific survival
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FACT-G	Functional Assessment of Cancer Therapy- General
FDG	Fluorodeoxyglucose
FEV	Forced expiratory volume
FRS	Fractions
FU	Followup
GTV	Gross tumor volume
GY	Grays
HC	Histopathology confirmation
HDR	High-dose-rate
Hst	Histologically
IGRT	Image-Guided Radiotherapy
IMRT	Intensity-modulated radiotherapy
INR	International Normalized Ratio
KFI	Kaplan-Feinstein index
KPS	Karnofsky performance status
LB	Lobar bronchus
LC	Lung cancer
LCC	Large cell carcinoma
LCS	Lung Cancer Subscale
LCT	Local control
LENT-SOMA	Late Effects Normal Tissue Task Force -Subjective, Objective, Management, Analytic *scales*
LL	Lower lobe
MB	Main bronchus
MCS	Mental Component Summary
MeV	Million electron volts
MI	Myocardial Infarction
ML	Middle lobe
mos	Months

MS	Main stem
N	Number
NA	Not applicable
NCI	National Cancer Institute
NOS	Not otherwise specified Non-Small Cell Lung Cancer
NR	Not reported
NSCC	Non squamous cell lung cancer
NSCLC	Non-small cell lung cancer
NSS	Not statistically significant
OMC	Other Medical Comorbidities
OS	Overall Survival
PCS	Physical Component Summary
PET	Positron Emission Tomography
PHDT	Photodynamic therapy
PFS	Progression-free survival
PRO	Prospective
PS	Performance status
Pts	Patients
PTV	Planning target volume
PVD	Peripheral Vascular Disease
QLQ	Quality of life Questionnaire
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RET	Retrospective
RFA	Radiofrequency ablation
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
Rx	Treatment
SAS	Single arm study
SB	Superior bronchus
SBRT	Stereotactic body radiotherapy
SCC	Squamous cell carcinoma
SCS	Simplified comorbidity score
SWOG	Southwest Oncology Group
TOI	Trial Outcome Index
UICC	Union Internationale Contre le Cancer
UL	Upper lobe
UNSCLC	Unclassified Non-Small Cell Lung Cancer
WHO	World Health Organization
YAGL	Yttrium aluminum garnet laser

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