



Effective Health Care Program

Comparative Effectiveness Review
Number 112

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



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

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This report is based on research conducted by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10058-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

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 can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. 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 email to epc@ahrq.hhs.gov.

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In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

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

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

Structured Abstract

Objectives. We prepared this report on the comparative effectiveness and harms of lung-directed nonsurgical therapies for non–small-cell lung cancer (NSCLC) in three distinct patient populations: (1) patients with stage I NSCLC who are not surgical candidates (Key Question 1), (2) patients with stage I NSCLC who are deemed operable but decline surgery (Key Question 2), and (3) patients with endoluminal NSCLC causing obstruction (Key Question 3). For stage I NSCLC, the local nonsurgical interventions could include conformal radiotherapy modalities and radiofrequency ablation (RFA). For patients with airway obstruction due to an endoluminal NSCLC, local nonsurgical interventions could include those for the stage I setting, as well as conventional wide-field radiotherapy, brachytherapy, laser and mechanical debridement, endoluminal stents, cryoablation, and photodynamic therapy. Surgical resection of any type is not considered as a comparator for any of the Key Questions.

Data sources. MEDLINE[®], Embase[®], and the Cochrane Controlled Trials Registry were searched from January 1, 1995, to July 25, 2012. A search of the gray 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 for each Key Question by a team of reviewers, with independent data verification. Study quality and the risk of bias of randomized controlled trials (RCTs) were assessed using the United States Preventive Services Task Force criteria. The quality and risk of bias of single-arm studies were assessed using the Carey and Boden criteria. The strength of the body of evidence was assessed according to the Agency for Healthcare Research and Quality Methods Guide.

Results. In our searches, we identified 4,648 unique titles and screened 1,178 in full text. Of the latter, 55 met the inclusion criteria. Thirty-five studies were relevant to Key Question 1, considering medically inoperable patients with stage I NSCLC; 6 were relevant to Key Question 2, considering medically operable patients with stage I NSCLC who decline surgery; and 17 were relevant to Key Question 3, considering patients with inoperable endoluminal NSCLC causing symptoms of obstruction. Three studies addressed both Key Questions 1 and 2. All studies relevant to Key Questions 1 and 2 were single-arm design, prospective (n=15), retrospective (n=21), or not specified (n=2). Among 17 papers included for Key Question 3, 5 were RCTs, 1 was a nonrandomized comparative study, and 11 were single-arm studies. Because comparative study evidence on RFA and debridement and stenting was unavailable for Key Question 3, we included evidence from two single-arm studies involving stents and one on RFA. All RCTs were of poor quality. Only one comparison was available per study, with no two studies examining the same set of interventions. Outcomes of therapy for all Key Questions included overall survival, adverse effects, and quality of life.

Conclusions. Evidence on localized nonsurgical therapies for patients with stage I NSCLC who are not surgical candidates or who decline surgery consists only of single-arm studies, with no direct comparisons among interventions. The best evidence for NSCLC patients with endoluminal obstruction consists of poor-quality single RCTs for each comparison; we did not identify evidence that permitted us to draw conclusions based on indirect comparisons. Overall, evidence is insufficient to permit conclusions on the comparative effectiveness of local nonsurgical therapies for inoperable or operable patients with stage I NSCLC or inoperable NSCLC patients with endoluminal tumor causing pulmonary symptoms.

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Executive Summary

Background

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

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

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

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

Treatment Options for NSCLC

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

- Surgically resectable disease (generally stage I, stage II, and selected stage III tumors)
- Potentially operable or inoperable locally (T3–T4) or regionally (N2–N3) advanced disease, including endoluminal lesions
- Inoperable distant metastatic disease, including distant metastases (M1) that are found at the time of diagnosis

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

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

Local Nonsurgical Treatment Options for Stage I NSCLC

Radiotherapy has a role in the definitive treatment of patients with stage I NSCLC who are deemed medically inoperable or those who decline surgery.^{7,9} Ideally, radiotherapy balances delivery of a cytotoxic dose of ionizing radiation to the tumor volume, attempting to minimize adverse effects of radiation on adjacent normal lung tissue and thoracic structures. Several radiotherapy modalities have been used to treat patients with stage I NSCLC. Conventional wide-field two-dimensional radiation therapy (2DRT) has been used extensively to treat medically inoperable patients with stage I NSCLC. Delivery of radiation to a total dose that ranged from 31 to 103 Gray (Gy), in daily fractions of 1.8-2 Gy, has been reported to produce overall survival rates of 17 percent to 42 percent among patients with early-stage disease.⁸ However, conventional 2DRT is no longer in routine use in modern radiation oncology practice in this setting and thus was not considered in this comparative effectiveness review (CER).

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

purposes of this report, we use the term “SBRT.” Charged particle–based therapy such as proton beam radiotherapy (PBRT) is also available.¹⁵

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

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

Local Nonsurgical Treatment Options for Symptomatic Endobronchial NSCLC

Patients with airway obstruction from nonresectable primary or recurrent endoluminal lung tumors comprise 20–30 percent of NSCLC cases and manifest symptoms of disabling dyspnea, cough, and hemoptysis.^{23,24} Up to 40 percent of lung cancer deaths may be attributed to such locoregional disease. Management of these patients is a significant challenge. For example, the ability to promptly alleviate airway distress may be lifesaving, as some patients may succumb to suffocation within hours of presentation.^{24–26} Patients with such advanced disease often require emergency treatment to relieve airway obstruction or stop bleeding. These interventions are palliative but are performed in some patients with curative intent.

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

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

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

Several interventional methods involve tumor debulking to palliate symptoms in patients with advanced endobronchial NSCLC.^{19,25,26,28} Interventional bronchoscopy with mechanical tumor debridement and stent placement can rapidly reestablish airway patency and relieve dyspnea and respiratory distress in patients with airway obstruction due to a malignant

endoluminal tumor.^{25,28} Debridement and stent placement may be complemented by subsequent application of radiotherapy to extend the durability of palliation and may offer definitive therapy for local tumors.

Laser resection involving the neodymium-doped yttrium aluminum garnet (Nd-YAG) laser and photodynamic therapy (PDT) using porfimer sodium have been investigated in this setting, with suggestion of symptomatic improvement in some cases.¹⁹ RFA also has been used in cryosurgery.

Objectives

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

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

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

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

Key Questions and Analytical Framework

The Key Questions and CER analytical frameworks (Figures A and B) are structured to be consistent with the populations, interventions, comparisons, outcomes, timing, and settings (PICOTS) framework (Table A), as laid out in the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” (Methods Guide).²⁹

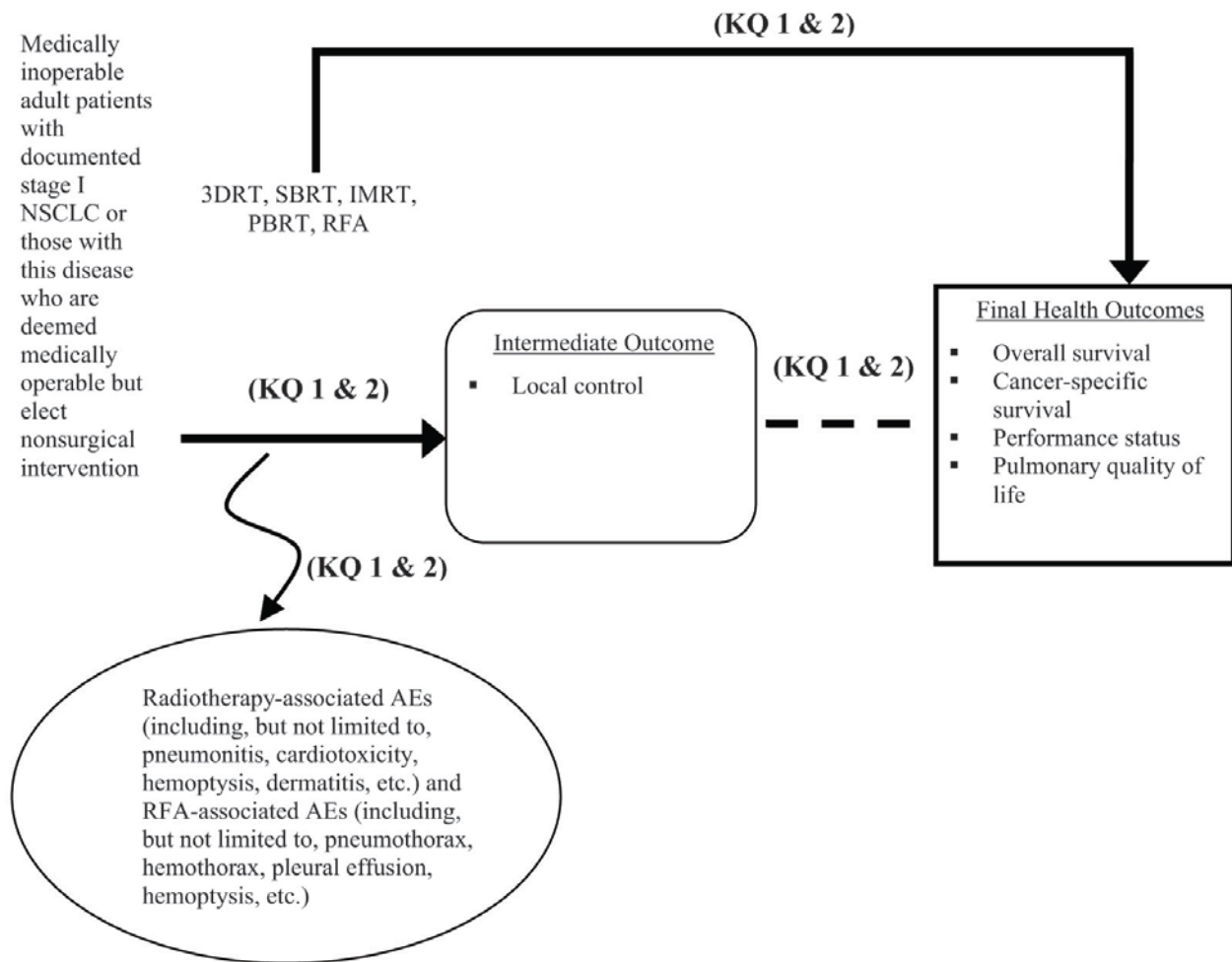
The Key Questions are:

Key Question 1. What are the comparative benefits and harms of local nonsurgical definitive therapies for documented (clinical or biopsy) stage I (T1N0M0, T2N0M0) NSCLC in adult patients (age 18 years or older) who are not surgical candidates because of the presence of contraindications to major surgery—for example, cardiac insufficiency, poor pulmonary function, presence of severe intercurrent illness, or poor performance status?

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

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

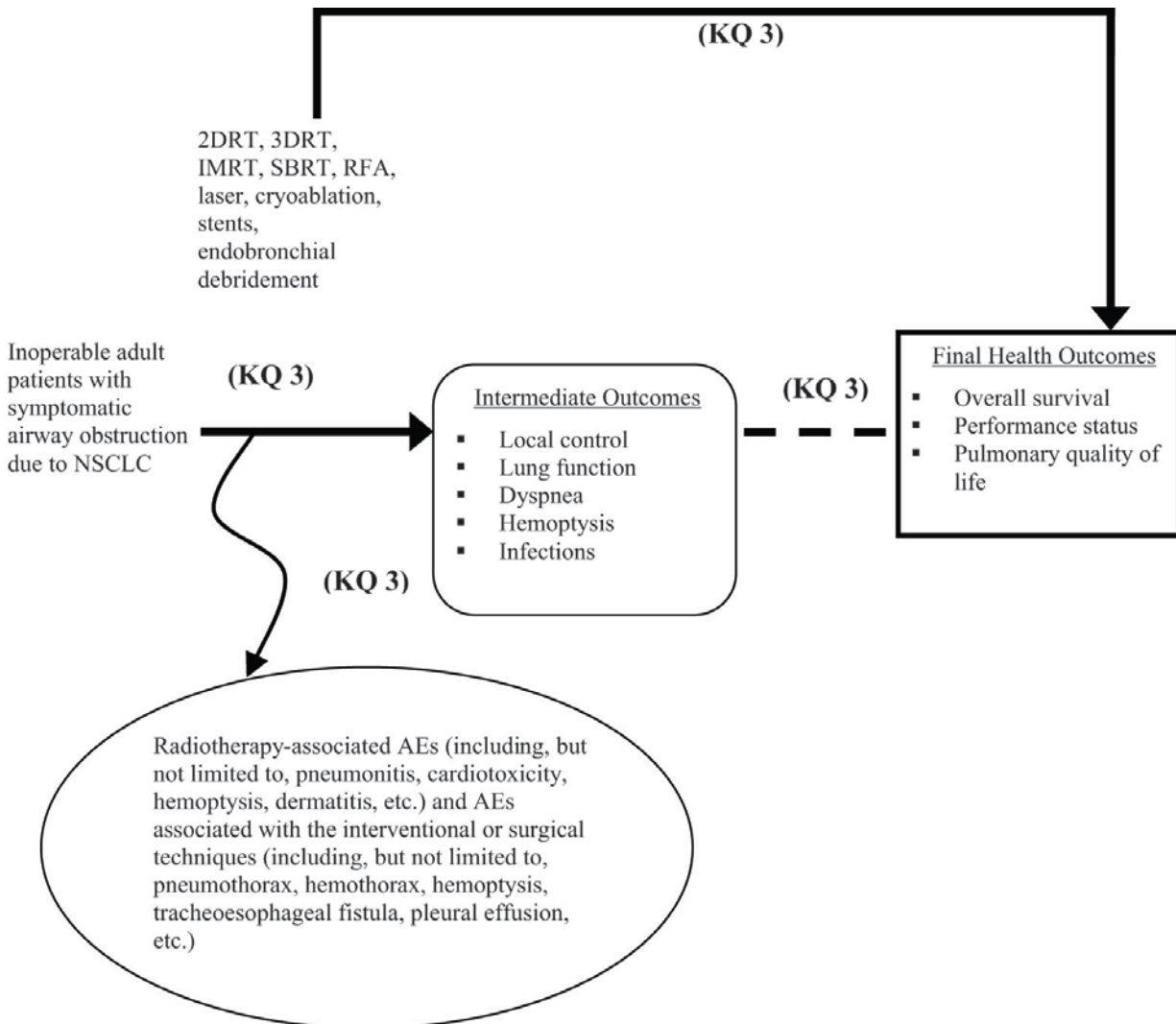
Figure A. Analytical framework for comparative effectiveness of local nonsurgical definitive therapies for adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 or T2N0M0) medically inoperable NSCLC or those with documented stage I NSCLC who are deemed operable but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



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

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

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



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

Table A. PICOTS for the Key Questions

| PICOTS | Key Questions 1 and 2 | Key Question 3 |
|---------------------|---|--|
| Population | <p>Key Question 1: Adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 and T2N0M0) NSCLC not deemed surgical candidates because of the documented presence of contraindications to major surgery—for example, cardiac insufficiency, poor pulmonary function, severe intercurrent illness, or poor performance status</p> <p>Key Question 2: Adult patients (age 18 years or older) with documented (clinical or biopsy) stage I (T1N0M0 and T2N0M0) NSCLC who would be deemed surgical candidates according to current clinical criteria but decline surgery</p> | <p>Adult patients (age 18 years or older) with endoluminal NSCLC causing obstruction of the trachea, main stem, or lobar bronchi and recurrent or persistent thoracic symptoms such as hemoptysis, cough, dyspnea, and postobstructive pneumonitis who were treated with curative or palliative intent</p> |
| Intervention | <p>All interventions are first-line (definitive), nonsurgical therapies:</p> <ul style="list-style-type: none"> • Conformal external-beam radiotherapy methods (including SBRT, 3DRT, and IMRT) • PBRT • RFA | <ul style="list-style-type: none"> • Conventional 2DRT • Conformal PBRT methods (including SBRT, 3DRT, and IMRT) • Brachytherapy • RFA • Cryoablation • Laser therapy • Endobronchial debridement and stents • PDT • Electrocautery • Combinations—for example, endobronchial debridement plus a stent compared with debridement alone or combination of 2DRT with brachytherapy compared with radiotherapy alone • Because systemic therapy (chemotherapy) is used with radiotherapy or local nonsurgical interventional methods in stage III or greater patients, we collected information on chemotherapy to use in categorizing and assessing outcomes to ensure that relevant and appropriate comparisons are made, particularly as they relate to possible harms. Such comparisons may be segregated and reported accordingly if it is not possible to discern interventional therapeutic effects |
| Comparator | <ul style="list-style-type: none"> • Comparators comprise the interventions noted above | <ul style="list-style-type: none"> • Comparators comprise the interventions noted above |
| Outcome | <ul style="list-style-type: none"> • Final health outcomes: OS, CSS, performance status, pulmonary QOL • Intermediate outcomes: LCT • Adverse outcomes: Radiotherapy-associated AEs (including, but not limited to, pneumonitis, cardiotoxicity, hemoptysis, dermatitis, etc.) and RFA-associated AEs (including, but not limited to, pneumothorax, hemothorax, hemoptysis, pleural effusion, etc.) | <ul style="list-style-type: none"> • Final health outcomes: OS, performance status, pulmonary QOL • Intermediate outcomes: LCT, lung function, pulmonary symptoms (e.g., dyspnea, hemoptysis), respiratory tract infection • Adverse outcomes: Radiotherapy-associated AEs (including, but not limited to, pneumonitis, cardiotoxicity, hemoptysis, dermatitis, etc.) and AEs associated with the interventional or surgical techniques (including, but not limited to, pneumothorax, pleural effusion, hemoptysis, transesophageal fistula, pericardial effusion) |

Table A. PICOTS for the Key Questions (continued)

| PICOTS | Key Questions 1 and 2 | Key Question 3 |
|----------------|---|---|
| Timing | <ul style="list-style-type: none"> The relevant periods occur from the time of treatment through followup over months (palliation) or years (OS) | <ul style="list-style-type: none"> The relevant periods occur from the time of treatment through followup over months (palliation) or years (OS) |
| Setting | <ul style="list-style-type: none"> Inpatient and outpatient | <ul style="list-style-type: none"> Inpatient and outpatient |

2DRT = two-dimensional radiotherapy; 3DRT = three-dimensional radiotherapy; AE = adverse event; CSS = cancer-specific survival; IMRT = intensity-modulated radiotherapy; LCT = local control; NSCLC = non-small-cell lung cancer; OS = overall survival; PBRT = proton beam radiotherapy; PDT = photodynamic therapy; PICOTS = population, intervention, comparator, outcome, timing, and setting; QOL = quality of life; RFA = radiofrequency ablation; SBRT = stereotactic body radiotherapy
 Note: T, N, and M refer to tumor, lymph node involvement, and metastasis in the TNM staging system.

Methods

Input From Stakeholders

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

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

Data Sources and Selection

A medical librarian conducted electronic searches of MEDLINE[®], Embase[®], and the Cochrane Controlled Trials Registry, seeking randomized, nonrandomized comparative, and observational studies published between January 1, 1995, and July 25, 2012. We truncated the search at 1995 to ensure comparability of procedures and technologies. The search was limited to English-language studies based on the following rationale. First, evidence suggests that language restrictions do not change results of systematic review for conventional medical interventions.³⁰ Second, input from the TEP suggested that most if not all of the pivotal studies in this area would be captured in the English-language evidence base and that restriction to English would not introduce bias. Our search strategy used the National Library of Medicine’s Medical Subject Headings (MeSH[®]) keyword nomenclature developed for MEDLINE[®] and adapted for use in other databases. The full search strings and strategies are listed in Appendix A of the full report.

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

Inclusion Criteria

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

Key Questions 1 and 2

- Study included medically inoperable NSCLC stage I patients (T1N0M0 and T2N0M0) or medically operable NSCLC stage I patients (T1N0M0 and T2N0M0) who refuse surgery
- Such patients received only one of the following local nonsurgical interventions as first-line (definitive) treatment:
 - Conformal radiotherapy methods (including SBRT, 3DRT, IMRT)
 - PBRT
 - RFA
- Study reported ≥ 1 of the following types of outcome data for such patients:
 - Survival outcome (overall survival or cancer-specific survival)
 - Local control (an outcome defined as the arrest of cancer growth at the site of origin)
 - Pulmonary quality of life (QOL)
 - AEs specific to radiotherapy techniques or to RFA

Key Question 3

- Study included NSCLC patients of any stage with a symptomatic endoluminal obstruction
- Such patients received ≥ 1 of the following local nonsurgical interventions:
 - Conformal radiotherapy methods (including SBRT, 3DRT, IMRT)
 - Conventional 2DRT
 - PBRT
 - RFA
 - Brachytherapy
 - Cryoablation
 - Laser therapy, including PDT
 - Electrocautery
 - Endobronchial debridement and stents
- Study reported data ≥ 1 of the following types of outcome data for such patients:
 - Survival outcome (overall survival or cancer-specific survival)
 - Local control (an outcome defined as the arrest of cancer growth at the site of origin)
 - Symptom relief
 - Pulmonary QOL
 - AEs specific to radiotherapy or interventional techniques (e.g., RFA, cryoablation, electrocautery) or to surgical techniques (laser or mechanical debridement and stents)

Exclusion Criteria

- Editorials, commentaries, abstracts, animal studies, case reports, non-English-language, and diagnostic accuracy studies were excluded.
- Primary studies published prior to January 1, 1995, were excluded.

- If we identified more than one article that included the same patients, interventions, and outcomes, we included the article with the longest followup, excluding the earlier paper(s). The latter were cross-indexed in the abstraction tables.
- For Key Questions 1 and 2, we compared single interventions—for example, two different conformal radiotherapy methods, or RFA compared with a conformal radiotherapy method. We excluded studies that used any postintervention systemic (e.g., chemotherapy) or local nonsurgical therapy but did not define the therapy or disaggregate the clinical outcomes of such patients. Failure to stratify or disaggregate outcome data according to the treatment received—for example, a local nonsurgical intervention with subsequent chemotherapy at progression—precludes determining whether an outcome such as overall survival could be attributed to the local intervention, the chemotherapy, or the combined effect of both therapies.

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

Data Abstraction and Quality Assessment

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

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

The main data elements for the CER were abstracted directly into Microsoft Word[®] tables. Other elements and the study risk-of-bias assessments were abstracted in DistillerSR. The evidence tables were divided by Key Question and assigned for abstraction to all team members. One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second reviewed the articles and evidence tables for accuracy. Disagreements were resolved by discussion, and if necessary, by consultation with a third reviewer.

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

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

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

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

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

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

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

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

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

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

Data Synthesis and Analysis

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

Assessment of the Strength of Evidence

We graded the strength of the overall body of evidence for overall survival, symptom relief, quality of life, and harms. The system used for rating the strength of the overall body of evidence is outlined in the AHRQ Methods Guide²⁹ and based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.³³ We also used the GRADE guideline on assessing the risk of bias.³⁴ This system explicitly addresses four required domains: risk of bias, consistency, directness, and precision. Two independent reviewers rated all studies on domain scores and resolved disagreements by consensus discussion; the same reviewers also used the domain scores to assign an overall SOE grade.

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

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

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

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

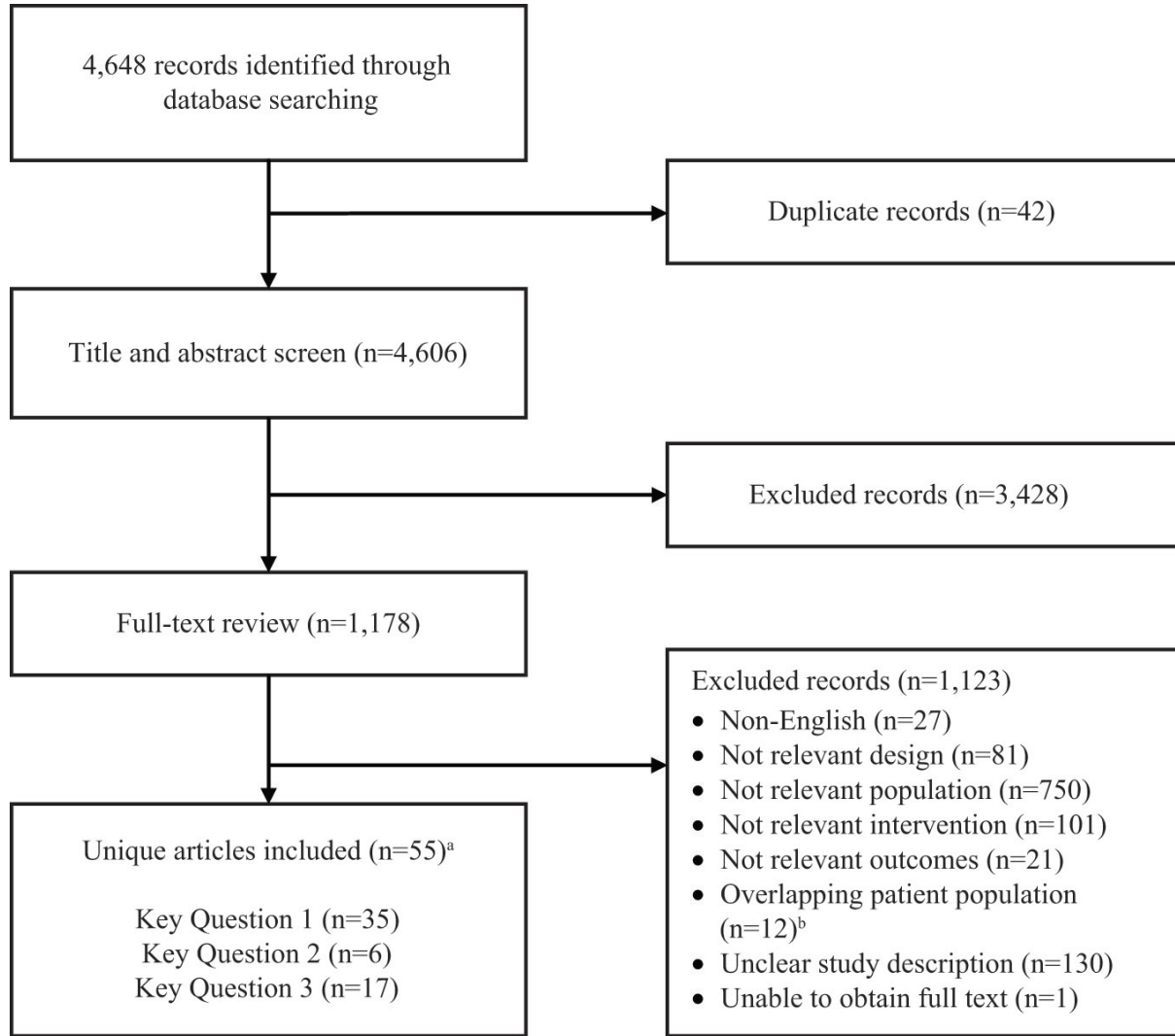
Results

Overview

Of the 4,648 unique titles identified, we screened 1,178 in full text. Of these, 55 met the CER inclusion criteria; 35 were relevant to Key Question 1, 6 were relevant to Key Question 2, and 17 were relevant to Key Question 3. Three studies addressed both Key Questions 1 and 2. Details are given in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)³⁵ diagram (Figure C). All studies relevant to Key Questions 1 and 2 were single-arm design, prospective (n=15), retrospective (n=21), or not specified (n=2). Among 17 papers

included for Key Question 3, 5 were RCTs, 1 was a nonrandomized comparative study, and 11 were single-arm studies.

Figure C. PRISMA diagram for disposition of literature search results



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

^aThree studies addressed both Key Questions 1 and 2.

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

Key Points

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

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

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

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

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

- All six RCTs included in this report were of poor quality according to the USPSTF rating criteria. Further analysis is provided in the Discussion section that follows.
- Evidence from six comparative studies is insufficient to draw conclusions about relative benefits and harms of six unique treatment comparisons (brachytherapy plus EBRT vs. brachytherapy alone, brachytherapy plus EBRT vs. EBRT alone, brachytherapy vs.

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

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

Discussion

Strength of Evidence

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

Key Question 1

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

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

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

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

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

Key Question 2

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

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

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

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

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

Key Question 3

Overall, the evidence from RCTs is insufficient to form conclusions about the benefits (symptom relief, survival) and harms (treatment-related toxicities) of local nonsurgical therapies (brachytherapy plus EBRT vs. brachytherapy alone, brachytherapy plus EBRT vs. EBRT alone, brachytherapy vs. EBRT, laser plus brachytherapy vs. laser alone, laser vs. electrocautery, laser vs. PDT) in symptomatic inoperable patients with obstructive endoluminal NSCLC. The strength of evidence for the six included RCTs is summarized in Table D.

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

Brachytherapy Plus EBRT Versus Brachytherapy Alone

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

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

Brachytherapy Plus EBRT Versus EBRT Alone

The evidence for this comparison comprised one small RCT³⁷ (n=95). This trial was considered to have a high risk of bias, primarily because the trial was discontinued prematurely

due to lack of patient accrual and was underpowered to detect a difference in the rate of the primary endpoint (rate of dyspnea). The consistency of the evidence was unknown, as it was a single RCT without confirmation from any other study. The outcomes measured in the study—symptom relief, survival, and treatment-related toxicities—were all direct. The evidence for symptom relief, survival, and treatment-related toxicities was imprecise.

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

Brachytherapy Versus EBRT

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

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

Laser Plus Brachytherapy Versus Laser Alone

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

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

Laser Versus PDT

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

outcomes measured in the study—survival and treatment-related toxicities—were all direct. The evidence for treatment-related toxicities was imprecise, while it was precise for survival.

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

Laser Versus Electrocautery

The evidence for this comparison comprised one small nonrandomized comparative study⁴¹ (n=29). This study was considered to have serious risk of bias, primarily because of lack of adjustment for any potential confounders. A disproportionate number of patients had received previous treatment in the laser-treated group (93%) compared with the electrocautery group (53%). Further, the mean time from diagnosis to study treatment was different in the two groups (4.7 months in the laser group vs. 7.5 months in the electrocautery group). The consistency of the evidence was unknown, as it was a single nonrandomized comparative study without confirmation from any other study. The outcomes measured in the study—survival and symptom relief—were direct. The evidence for symptom relief and survival was imprecise.

Because the evidence base that addressed these outcomes consisted of a nonrandomized comparative study, the starting level of SOE was low. SOE was reduced by two levels based on very serious risk of bias and by one level each for unknown consistency and imprecision. Therefore, the SOE is insufficient that, compared with electrocautery, laser therapy improves survival and symptom relief.

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

| Treatment and Evidence Base | Outcome | Unit of Measure | Risk of Bias | Consistency | Directness | Precision | Overall Strength of Evidence |
|---|--------------------|--|--------------|-------------|------------|-----------|------------------------------|
| Brachytherapy plus EBRT vs. brachytherapy alone (1 RCT, n=45) | Symptom relief | Incidence and response rate | High | Unknown | Direct | Imprecise | Insufficient |
| | QOL | EORTC QLQ-C30 & LC 13 V3.0 instruments | | | | | |
| | Treatment toxicity | Incidence of Grade ≥II RTOG morbidity scoring criteria | | | | | |
| Brachytherapy plus EBRT vs. EBRT alone (1 RCT, n=95) | Symptom relief | Response rate | High | Unknown | Direct | Imprecise | Insufficient |
| | Survival | Overall survival | | | | | |
| | Treatment toxicity | Incidence | | | | | |
| Brachytherapy vs. EBRT (1 RCT, n=99) | Symptom relief | % improvement | High | Unknown | Direct | Imprecise | Insufficient |
| | Survival | Overall survival | High | Unknown | Direct | Precise | Insufficient |
| | Treatment toxicity | Incidence | High | Unknown | Direct | Imprecise | Insufficient |

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

| Treatment and Evidence Base | Outcome | Unit of Measure | Risk of Bias | Consistency | Directness | Precision | Overall Strength of Evidence |
|--|--------------------|------------------|--------------|-------------|------------|-----------|------------------------------|
| Nd-YAG plus brachytherapy vs. Nd-YAG alone (1 RCT, n=29) | Symptom relief | Speiser's index | High | Unknown | Direct | Imprecise | Insufficient |
| | Survival | Overall survival | | | | | |
| | Treatment toxicity | Incidence | | | | | |
| Photodynamic therapy vs. laser (1 RCT, n=31) | Survival | Overall survival | High | Unknown | Direct | Precise | Insufficient |
| | Treatment toxicity | Incidence | High | Unknown | Direct | Imprecise | Insufficient |
| Nd-YAG vs. electrocautery (1 NRC, n=29) | Survival | Mean survival | High | Unknown | Direct | Imprecise | Insufficient |
| | Symptom relief | % response | | | | | |

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

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

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

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

Applicability of the Findings

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

Key Questions 1 and 2

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

The degree to which the data presented in this report are applicable to clinical practice is a function of the similarity between populations in the included studies and the patient population that receives clinical care in diverse settings. It also is related to the relative availability of the interventions. The literature base is observational, lacking comparative evidence. Case series are

descriptive studies that are limited in their ability to control for biases. Selection bias is of particular concern, as patients receive treatment based on clinician preferences, center resources, and patient characteristics and preference rather than random allocation. This evidence base is therefore insufficient to support any attempt to draw comparative conclusions.

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

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

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

| Domain | Applicability of Evidence |
|---------|---|
| Setting | <ul style="list-style-type: none"> The evidence for KQ1 and KQ2 is international, primarily obtained in tertiary institutional settings. More sophisticated interventions such as IMRT and SBRT require an institutional commitment to quality assurance and ongoing training that may be difficult to achieve in smaller community-based centers. We did not collect or analyze information to examine these issues. |

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

Key Question 3

Multiple shortcomings of the current evidence base for Key Question 3 preclude interpretation about general applicability. First, the comparative benefits and harms of various endobronchial treatments are still unknown because of the lack of good-quality RCTs. The available studies were all poor quality, and often were small and not powered to detect a prespecified clinically meaningful difference in a standardized outcome of interest. Second, patient characteristics were poorly defined. The majority of studies did not report performance status, and therefore it is difficult to assess the relative health and activity level of these patients and to whom this limited evidence applies. Third, there was a wide variation in the outcome measures to report symptom relief in the current studies. Fourth, many studies did not report the frequency, process, or method of assessing severity of treatment-related toxicities, and therefore the true harms associated with these interventions are likely to be underrepresented in the current data. Some factors that affect applicability of the findings of this CER are summarized in Table G for Key Question 3.

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

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

Table G. Summary of applicability of evidence for Key Question 3 (continued)

| Domain | Applicability of Evidence |
|---------------|--|
| Timing | <ul style="list-style-type: none">• The relevant periods occur from the time of treatment through followup over months (palliation) or years (overall survival). |
| Setting | <ul style="list-style-type: none">• The outcomes of local bronchoscopic therapies largely depend on the expertise of the provider and the center providing these services. We could not assess the impact of such operating characteristics on the treatment outcomes because these data were not available in the published papers. |

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

Findings in Relationship to What Is Already Known

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

Limitations of Current Review and Evidence Base

Key Questions 1 and 2

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

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

Key Question 3

The body of evidence available for Key Question 3 comprised five RCTs, one nonrandomized comparative study, and three relevant single arms from three otherwise

comparative studies. We included the latter three study arms because we did not have higher level evidence for the interventions in question, debridement and stenting. Significant limitations in the quality and quantity of the evidence base led us to conclude that the evidence was insufficient to make conclusions about the comparative effectiveness of local nonsurgical interventions to treat endobronchial obstructions in NSCLC patients. There was only one comparative study available to draw inferences about comparative effectiveness for six unique treatment comparisons. Therefore, the consistency domain for SOE was unknown. All six studies received a low rating in terms of USPSTF study quality; often the studies were small and not powered to detect a prespecified clinically meaningful difference in a standardized outcome of interest, thereby limiting their utility beyond hypothesis generation. Most studies lacked details about randomization and allocation concealment. The one nonrandomized comparative study available for Key Question 3 did not use statistical adjustment to reduce confounding; such adjustment for confounding should be consistently used in nonrandomized studies.

Research Gaps

Key Questions 1 and 2

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

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

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

- To assure comparability of patients and minimize bias, standardized patient selection criteria would be used that involve consultation, including a thoracic surgeon, medical oncologist, and radiation oncology specialist. Key factors to consider include comorbidity status (particularly cardiopulmonary function and capacity), age, performance status, tumor size, and tumor location.
- Standardized intervention protocols with training and quality assurance programs within and across participating institutions are necessary for the best study. For radiotherapy, key factors would include the imaging and planning method, immobilization method, dose and fractionation schedule, and the biologically effective dose (BED) for comparisons of different modalities (e.g., SBRT, 3DRT, IMRT, and PBRT). For RFA,

issues would include treatment power and duration in the context of tumor size and location.

- Prespecified followup criteria and methods—in particular, notation of subsequent systemic therapy administered at recurrence—are key considerations. Subsequent systemic therapy is a key concern because it is impossible to discern the effect of an intervention followed by systemic therapy at progression from that achieved with the intervention alone. Is the effectiveness a function of the systemic therapy, the intervention, or the combination?
- Rigorous and standardized reporting is needed to account for all patients and treatments received. Data for operable and inoperable patients would be reported separately. We urge that rigorous methods be used for the conduct of RCTs, particularly intent-to-treat analysis and adjustment of survival data to account for patients who develop recurrent disease and subsequently receive systemic chemotherapy as part of their treatment plan.
- Primary outcomes would include overall survival, cancer-specific survival, and local control. Prespecified systematic collection of AEs using validated criteria (e.g., Common Terminology Criteria for Adverse Events [CTCAE]) is necessary to permit accurate assessment of relative benefits and risks of the interventions.

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

The general dissemination of conformal radiotherapy technologies into community clinical practice, most lately and specifically SBRT,^{43,44} is a potential impediment to comparative study of those technologies. Published survey results show that nearly 40 percent of solo practitioners already treat patients with SBRT, which suggests that this technology is accessible and its efficacy accepted in the broader radiation oncology community.^{43,44} The shorter hypofractionated SBRT course is more “patient friendly” than those associated with conventionally fractionated conformal radiotherapy methods. This patient-specific advantage may represent an additional reason that SBRT has rapidly disseminated into clinical practice in the absence of direct comparative clinical trial evidence to support its reputation of clinical superiority over conventionally fractionated conformal techniques. We also recognize a number of other significant, perhaps insurmountable, technical impediments to conducting adequate comparative studies among the most widely available conformal radiotherapy-based modalities and other interventions such as RFA. These are outlined below.

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

clinically relevant comparisons between RFA and conformal radiotherapy-based treatments could be difficult.

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

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

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

Key Question 3

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

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

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

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

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

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

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

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

Conclusions

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

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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.¹ The disease arises from epithelial cells of the lung, from the central bronchi to terminal alveoli. The histological type correlates with site of origin, reflecting the variation in respiratory tract epithelium by location. The most common types of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, 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 adenocarcinoma in situ (formerly bronchioloalveolar carcinoma) usually arise in peripheral lung tissue. Adenocarcinomas are frequently associated with cigarette smoke, but may occur 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 nearly 70,000 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 T2a T2b | N1 N1 N0 | M0 M0 M0 |
| Stage IIB | T2b T3 | N1 N0 | M0 M0 |
| Stage IIIA | T1, T2 T3 T4 | N2 N1, N2 N0, N1 | M0 M0 M0 |
| Stage IIIB | T4 Any T | N2 N3 | M0 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 nonsurgical 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 are 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.⁶ 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.⁷ Data from the IASLC database of patients shows 5-year overall survival rates may range from 71 to 77 percent for stage IA NSCLC and 35 to 58 percent for stage IB disease.⁸ 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 of 80 percent and 72 percent, respectively.⁹

A comprehensive preoperative assessment must be performed to assess the risk for morbidity and mortality in NSCLC stage I patients being considered for curative-intent surgery.¹⁰ Surgical morbidity and mortality are typically low in most modern series in the stage I setting, with major complications reported in about 6 percent of lobectomy cases and 18 percent in pneumonectomy cases.¹¹ The estimated risk of surgical mortality should be less than 4 percent for lobectomy and less than 9 percent for pneumonectomy in order to proceed to surgery.^{7,10}

Local Nonsurgical Treatment Options for Stage I NSCLC

Surgery is the standard of care for patients with resectable stage I NSCLC. However, alternative treatments are needed for two subsets of stage I NSCLC patients. First is a subset that comprises about 20-30 percent of stage I patients, who have resectable tumors but are deemed medically inoperable due to comorbidities such as diminished cardiac reserve, poor pulmonary function, and poor performance status.^{7,12-14} A second, much less common subset comprises patients who are deemed operable but decline surgery. Medically inoperable patients are more likely to die from intercurrent illness than from lung cancer; however, evidence exists to question this assumption.⁷ 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.¹⁵ 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.¹⁶

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.¹⁷ These patients would not be considered for surgery, but would be offered nonsurgical options that are outlined in the following section of this report.

Radiotherapy

External-beam radiotherapy (EBRT) has a role in the definitive treatment of patients with stage I NSCLC who are deemed medically inoperable, or in those who decline surgery.^{7,13} Ideally, EBRT balances delivery of a cytotoxic dose of ionizing radiation to the tumor volume, attempting to minimize adverse effects (AEs) of radiation on adjacent normal lung tissue and thoracic structures. A “standard” total dose is typically 60 to 70 Gray (Gy), delivered in increments (fractions) over variable periods, depending on the technology that is used and the therapeutic intent. All available radiotherapy platforms use a medical linear accelerator to deliver photon radiation, typically in the energy range of 6-10 MeV. Several modalities have been used to treat patients with stage I NSCLC, as follows.

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

Conventional wide-field 2DRT has been used extensively to treat medically inoperable patients with stage I NSCLC. Delivery of radiation to a total dose that ranged from 31 to 103 Gy, in daily fractions of 1.8-2 Gy, has been reported to produce overall survival rates of 17 percent to 42 percent among patients with early stage disease.¹⁴ However, this technique is no longer in routine use in modern radiation oncology practice in this setting. Thus, it was not considered for the stage I setting in this comparative effectiveness review (CER).

External-Beam Conformal Radiotherapy Options

A quest to improve upon survival rates achieved with conventional 2DRT has led to development of conformal radiotherapy methods for definitive (curative) treatment of inoperable patients with stage I NSCLC. Conformal radiotherapy refers to modalities in which cytotoxic radiation beams are “shaped” to cover the tumor volume plus a surrounding tissue margin to treat microscopic disease that may reside there. Photon-based modalities include three-dimensional conformal radiation therapy (3DRT); intensity-modulated radiation therapy (IMRT); and stereotactic body radiation therapy (SBRT), which is also known as stereotactic ablative radiotherapy.¹⁸⁻²⁰ For purposes of this report, we will use the term “SBRT.” Charged particle-based therapy such as proton beam radiotherapy (PBRT) is also available.²¹

Three-dimensional Conformal Radiation Therapy (3DRT)

3DRT employs 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 highly focused beams of radiation that converge at the tumor site.¹² This allows accurate and precise conformity of the radiation to the tumor volume, with very rapid dose fall-off in surrounding normal lung parenchyma. A 3DRT treatment protocol typically comprises 25-40 fractions (usually 1.8-2 Gy) delivered over a period of 5-10 weeks.

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. A typical total dose of 60 to 70 Gy is usually delivered in 25-40 fractions over a period of 5-10 weeks. 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 a larger volume of lung receives a low radiation dose with IMRT, which may actually increase the rate of injury.¹⁹

Stereotactic Body Radiation Therapy (SBRT)

SBRT delivers very high, conformal ablative doses of radiation in fewer treatment sessions than other conformal modalities, with the potential to cause less damage to surrounding normal tissue.²² SBRT regimens generally deliver a total dose of 60 Gy at greater than 10 Gy per fraction. Four-dimensional monitoring of tumor motion during the breathing cycle is accomplished by using a number of imaging techniques (CT, X-ray, ultrasound) that depend on the platform, tracking on bony structures or implanted fiducials. SBRT can deliver very high biologically effective doses (BED) above 100 Gray equivalent (GyE) that are needed to ablate the tumor and sterilize the tumor margins, minimizing damage to adjacent normal tissue. Conventionally fractionated schemes, delivering a similar total dose in 25-40 fractions, typically do not reach a similar BED range.

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.²¹ 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.²¹

Summary: Radiotherapy

The optimal definitive external radiotherapy modality is not defined for patients with medical contraindications (medically inoperable patients) or for those with stage I NSCLC who elect nonsurgical treatment.²⁰ 3DRT and IMRT are distinguished from SBRT therapeutically primarily as a function of the fractionation schemes employed and the higher BED delivered to the tumor with SBRT compared to either 3DRT or IMRT. Technological distinctions include the methods or equipment used in patient positioning, patient immobilization, tumor tracking methods, control systems, beam collimation, and treatment-planning software. Conformal radiotherapy procedures are generally time-intensive, require significant training, and necessitate substantial advance planning.^{19,23} Institutional quality control processes are required to assure their safe and effective use, in particular IMRT.²⁴

Interventional Treatment Options

Interventional treatment options for stage I NSCLC include radiofrequency ablation (RFA).^{22,25} 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.²⁶ The most frequent complication of RFA is pneumothorax.²⁷

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.^{21,26,28}

Earlier brachytherapy was used as a definitive treatment of stage I nonsurgical patients, but is now considered appropriate only as an adjunct to surgery.²⁹ It was not considered in the stage I setting in this CER.

Local Nonsurgical Treatment Options for Symptomatic Malignant Endobronchial NSCLC

About 20 percent to 30 percent of NSCLC patients experience airway obstruction from non-resectable primary or recurrent lesions, with symptoms that may include disabling dyspnea, cough, and hemoptysis.^{30,31} Up to 40 percent of lung cancer deaths may be attributed to such locoregional disease. Management of these patients is a significant challenge. The ability to promptly alleviate airway distress may be lifesaving, as some patients may succumb to suffocation within hours of presentation.³¹⁻³³ Patients in this situation often require emergency treatment to relieve airway obstruction or to stop bleeding. Intervention typically is palliative, but may be performed with curative intent in some cases.

Radiotherapy

Patients with good performance status may benefit from EBRT (conventional 2DRT 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.³³ 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

Brachytherapy is another option for treating airway obstruction and can be used alone, or in combination with EBRT to boost the total dose of irradiation used.^{33,34} 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 brachytherapy, including massive hemoptysis, tracheoesophageal fistulas, bronchial stenosis and radiation bronchitis.³⁴

The role of brachytherapy 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. Brachytherapy 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 radiotherapy.³³

Bronchoscopy and Stents, Cryoablation and Photodynamic Therapy (PDT)

Several interventional methods are used to palliate symptoms in patients with an obstructive endobronchial NSCLC.^{25,32,33,35} Interventional bronchoscopy with mechanical tumor debridement and stent placement can rapidly reestablish airway patency and relieve dyspnea and respiratory distress in patients with airway obstruction due to a malignant endoluminal tumor.^{32,35} In a large cryosurgery series, 86 percent of 521 patients experienced improvement in one or more symptoms including cough, dyspnea, hemoptysis, and chest pain.³⁶ Laser resection involving the neodymium-doped yttrium aluminum garnet (Nd-YAG) laser and PDT using porfimer sodium have been investigated in this setting with suggestion of symptomatic improvement in some cases.²⁵ RFA also has been used in this setting.

Scope of the Review

This Agency for Healthcare Research and Quality (AHRQ) -sponsored CER of local nonsurgical 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 EBRT 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 nonsurgical modalities for inoperable patients in Key Question 1, and in operable patients who decline surgery in Key Question 2.

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

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

Key Questions

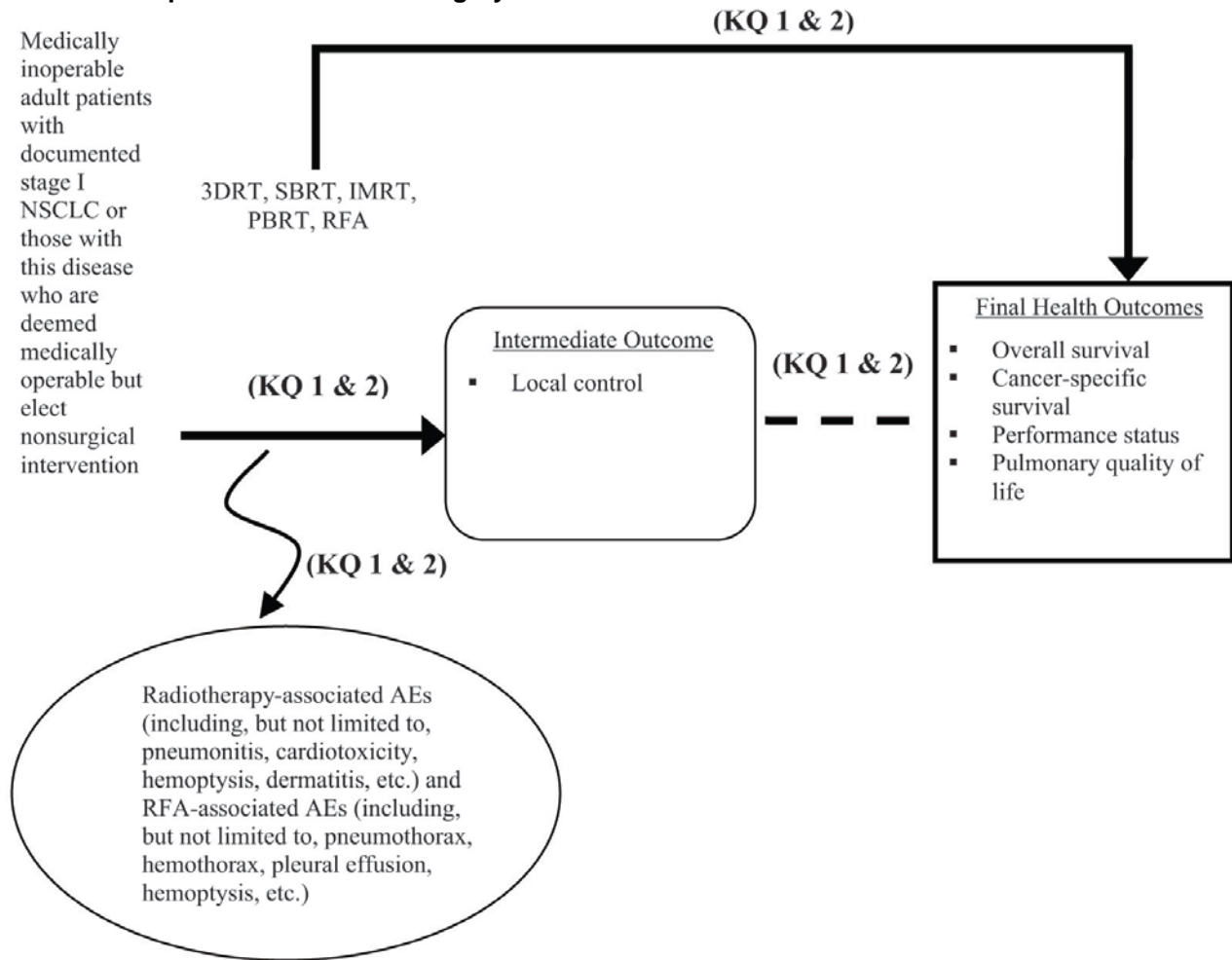
The Key Questions and CER analytical frameworks (Figure 1 and Figure 2) are structured consistent with the PICOTS (Populations, Interventions, Comparators, Outcomes, Timeframes, Settings) framework, as laid out in the AHRQ Evidence-based Practice Center (EPC) “Methods Guide for Effectiveness and Comparative Effectiveness Reviews”³⁷ (hereafter Methods Guide).

Key Question 1. What are the comparative benefits and harms of local nonsurgical definitive therapies for documented (clinical or biopsy) stage I (T1N0M0, T2N0M0) NSCLC in adult patients (age 18 years or older) who are not surgical candidates because of the presence of contraindications to major surgery, for example, cardiac insufficiency, poor pulmonary function, presence of severe intercurrent illness, or poor performance status?

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

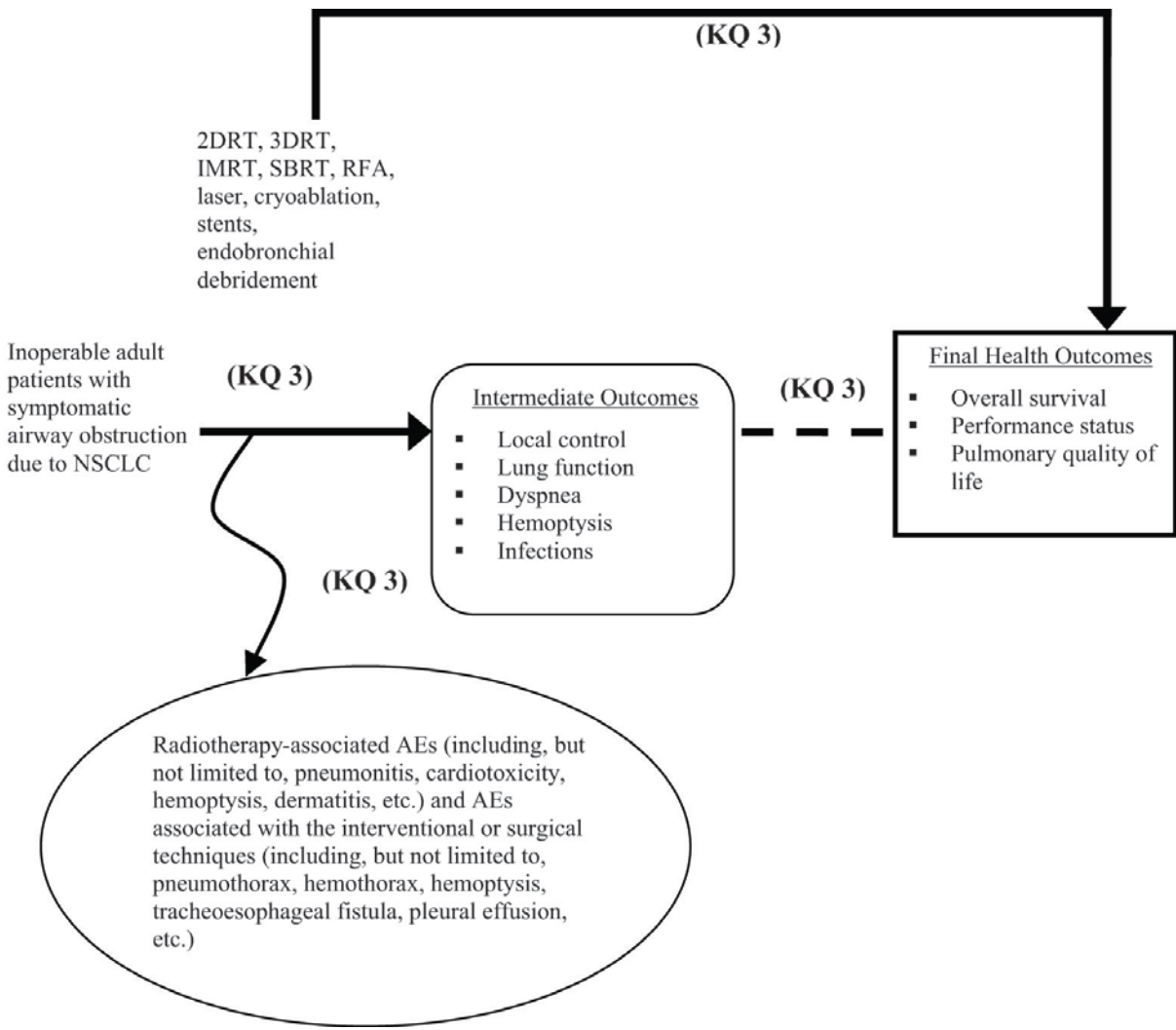
Key Question 3. What are the comparative short- and long-term benefits and harms of local nonsurgical therapies given with palliative or curative intent to patients with endoluminal NSCLC causing obstruction of the trachea, main stem, or lobar bronchi and recurrent or persistent thoracic symptoms such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

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 decline surgery



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

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



2DRT = two-dimensional, wide-field radiotherapy; 3DRT = three-dimensional radiotherapy; AE = adverse event; FEV = forced expiratory volume; IMRT = intensity-modulated radiotherapy; KQ = Key Question; NSCLC = non-small-cell lung cancer; PBRT = proton beam radiotherapy; RFA = radiofrequency ablation; SBRT = stereotactic body radiotherapy; YAG = yttrium aluminum garnet

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) NSCLC 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) NSCLC who would otherwise be deemed surgical candidates according to current clinical criteria but decline surgery.

Interventions

- Conformal radiotherapy methods (including SBRT, 3DRT, IMRT)
- PBRT
- RFA

Comparators

- Interventions were compared with each other as noted above.

Outcomes

- 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, radiotherapy-associated AEs (e.g., pneumonitis, cardiotoxicity, hemoptysis, dermatitis, etc.), non-radiotherapy-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 post obstructive pneumonitis, who were treated with curative or palliative intent.

Interventions

- Conventional 2DRT
- Conformal radiotherapy methods (including SBRT, 3DRT, IMRT)
- Brachytherapy
- RFA
- 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 radiotherapy alone.

Comparators

- Interventions were compared with each other as noted above.

Outcomes

- Final health outcomes: Overall survival, performance status, pulmonary quality of life
- Intermediate outcomes: Local control, lung function (e.g., forced expiratory volume [FEV1]), symptom relief (e.g., dyspnea, hemoptysis), respiratory tract infection
- Adverse outcomes: Includes, but not limited to, radiotherapy-associated AEs (e.g., pneumonitis, cardiotoxicity, hemoptysis, dermatitis, etc.), non-radiotherapy-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

This report is organized into three chapters: Methods, Results and Discussion. The Methods chapter describes the search strategy used to identify the published and unpublished evidence relevant to Key Questions, the processes used to systematically review and assess individual clinical studies for inclusion or exclusion, data elements that were abstracted from these articles to compile evidence tables and method use to assess quality ratings for individual studies as well as strength of evidence (SOE) ratings. The Results chapter is structured to sequentially address Key Questions 1, 2 and 3. Results of each Key Question include evidence summary tables, 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. The Discussion chapter addresses 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 chapter also addresses implications for policy decisions, in the context of limitations of the systematic review processes used and the evidence itself. This chapter concludes with a section 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.

Detailed 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 Guide³⁷ 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.³⁸

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 Evidence-based Practice Center (EPC) program, the role of Key Informant is to provide input in identifying relevant Key Questions for research that inform healthcare decisions. The EPC solicits input from the Key Informants when developing questions for systematic review or when identifying high priority research gaps and to identify topics for future research. Key Informants were not involved in analyzing the evidence or writing the report and have not reviewed the report except 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 Agency for Healthcare Research and Quality (AHRQ) Task Order Officer (TOO) and the EPC worked to balance, manage, or mitigate any potential conflicts of interest identified.

The draft Key Questions were posted on AHRQ's website for public comment on October 5, 2011 for 4 weeks. During this period, the EPC drafted a protocol for the CER and recruited a Technical Expert Panel (TEP) that comprised individuals with clinical expertise in radiation oncology, thoracic surgery and surgical oncology, pulmonology, and general oncology. The TEP provided input throughout the development of the review but was not involved in subsequent evidence analysis or drafting the report.

We received comments on the draft Key Questions, scope, and content of the proposed CER from several individuals and specialty societies. We addressed all the comments in discussions with the TOO and during conference calls with the TEP. Specifically, we eliminated a Key Question aimed at "technically inoperable" patients, and expanded the list of adverse events (AEs) we would attempt to capture for each intervention. The final protocol was posted on 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 July 25, 2012:

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

The search was limited to English language studies based on the following rationale. First, evidence suggests that language restrictions do not change results of systematic review for conventional medical interventions.³⁹ Second, input from the TEP suggested that most if not all of the pivotal studies in this area would be captured in the English language evidence base and that restriction to English 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), the 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 3 randomized controlled trials (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. Inclusion of medically inoperable NSCLC stage I patients (T1N0M0 and T2 N0M0) or medically operable NSCLC stage I patients (T1N0M0 and T2N0M0) who refuse surgery.
2. Such patients received only 1 of the following interventions:
 - Conformal radiotherapy methods (including stereotactic body radiotherapy (SBRT), three-dimensional conformal radiotherapy (3DRT), intensity-modulated radiotherapy (IMRT))
 - Proton beam radiotherapy (PBRT)
 - Radiofrequency ablation (RFA)
3. Reported data on one or more 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)
 - Pulmonary quality of life (QOL)
 - AEs

Key Question 3

1. Inclusion of NSCLC patients of any stage with a symptomatic endoluminal obstruction.
2. Such patients received 1 or more of the following interventions:
 - Conformal radiotherapy methods (including SBRT, 3DRT, IMRT)
 - Conventional 2D external beam radiotherapy (2DRT)
 - PBRT

- RFA
 - Brachytherapy
 - Cryoablation
 - Laser Therapy
 - Electrocautery
 - Endobronchial debridement and stents
3. 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
 - Pulmonary QOL
 - AEs

Exclusion Criteria

- Editorials, commentaries, abstracts, animal studies, case report, non-English language and 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 Key Question.
- For Key Questions 1 and 2, we compared single interventions, for example two different conformal radiotherapy methods, or RFA compared with a conformal radiotherapy method. We excluded studies that used any post-intervention systemic (e.g., chemotherapy) or local nonsurgical therapy but did not define the therapy or disaggregate the clinical outcomes of such patients.

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

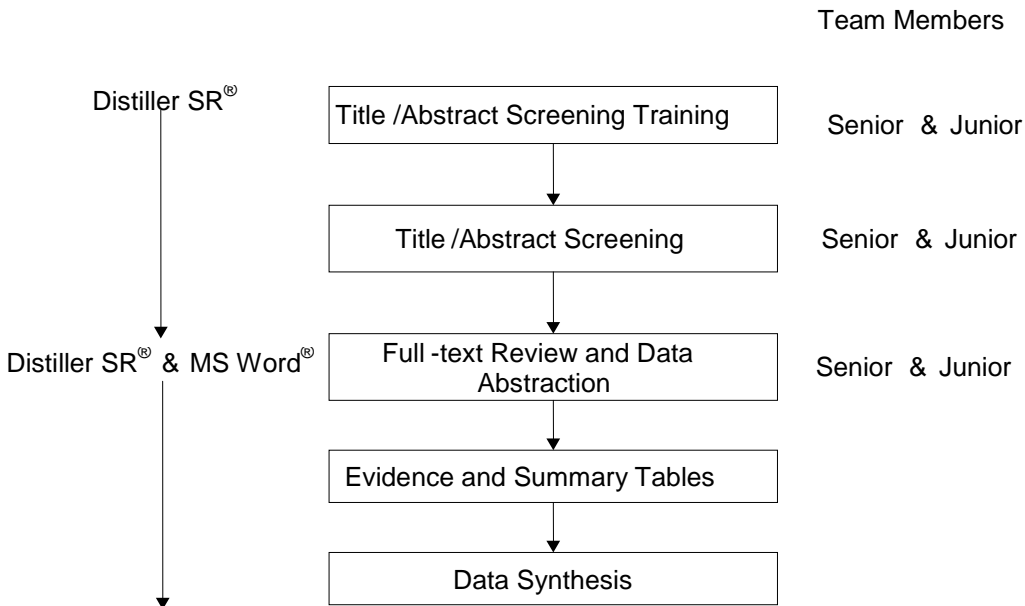
Study Selection Process

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; or 2) ineligible for full-text review. At least one training set (n=100) of representative titles and abstracts for each Key Question 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 two junior and one senior level team members. A reference was excluded only when both team members made independent decision to exclude it. In case of disagreement, the team leader adjudicated in consensus with all team members.

A test set of three references relevant to the three Key Questions 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 leader reviewed full-text articles independently to determine their inclusion in the systematic review. The reason for

exclusion of each full-text article reviewed was recorded in the Distiller SR[®] database. A paper could have been excluded for multiple reasons but only one reason was recorded. 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 and 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
 - Comorbidities
 - 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
- Followup and Evaluation Criteria
- Study Outcomes
 - Survival
 - Overall survival
 - Disease-specific survival
 - Local control
 - Lung Outcomes
 - Lung function
 - Obstructive symptoms
 - QOL
 - Performance status
 - Others
 - AEs

Quality (Risk of Bias) Assessment of Individual Studies

In adherence with the Methods Guide,³⁷ the risk of bias of individual comparative studies was assessed by the U.S. Preventive Services Task Force (USPSTF) criteria.⁴⁰ The quality of the

abstracted studies was assessed by one reviewer, and examined by the senior team member. 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.⁴¹

- 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.

The quality of the single-arm intervention studies was assessed by Carey and Boden criteria.⁴² These include eight criteria, which 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 eight 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 Key Questions, 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 Key Question 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 AHRQ Methods Guide³⁷ and based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.⁴³ Further, we also used the GRADE guideline on assessing the risk of bias.⁴⁴ 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 (SOE) grade.

The process of grading the body of evidence⁴³ was as follows. A body of evidence represented by RCT(s) would have a starting strength of high. A body of evidence represented by nonrandomized comparative studies would generally have a starting strength of low. For all study designs, the strength of evidence would be reduced by one level if there was high risk of bias, inconsistency or unknown consistency, indirectness and imprecision. Further, based on GRADE guidelines on assessing the risk of bias,⁴⁴ when the evidence was generated from studies that had very serious risk of bias, the strength of evidence was rated down by two levels. Case series or single-arm studies were deemed “indirect,” “imprecise” and “unknown” for the domains of “directness,” “precision” and “consistency.”

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

- **High.** High confidence that the evidence 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 PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting) framework.^{37,45,46} 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 were 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 were considered by the EPC in preparation of the final draft of the report. Peer Reviewers did not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments were documented and published after the publication of the evidence report.

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

Results

Introduction

Overview

This chapter presents the results of this comparative effectiveness review (CER) on local nonsurgical interventions for patients with non–small-cell lung cancer (NSCLC) in three distinct settings. Key Question 1 addresses interventions in patients with stage I disease who are deemed medically inoperable due to comorbidities that preclude definitive resection. Key Question 2 addresses local nonsurgical intervention in patients with stage I disease who are deemed medically operable but refuse surgery. Key Question 3 addresses evidence for the use of local nonsurgical 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 excluded studies are shown in Appendix B. We did not perform a quantitative data synthesis for any Key Question.

Results of Literature Searches

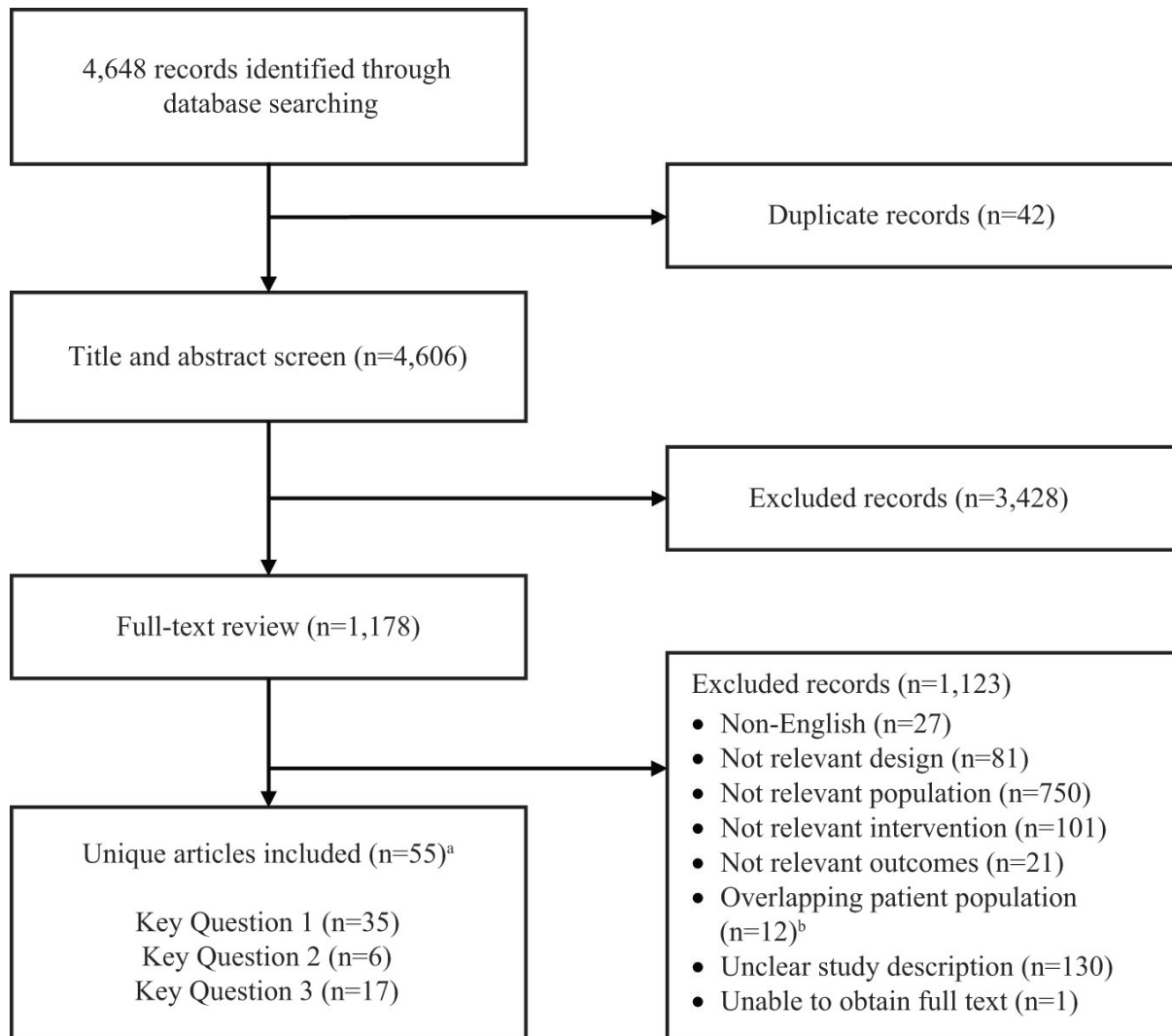
Electronic Search

Of the 4,648 unique titles identified, we screened 1,178 in full-text. Of these, 55 met the CER inclusion criteria: 35 were relevant to Key Question 1, six were relevant to Key Question 2 and 17 were relevant to Key Question 3. Three studies⁴⁷⁻⁴⁹ addressed both Key Questions 1 and 2. Details are given in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)³⁸ diagram (Figure 4). All studies relevant to Key Questions 1 and 2 were single-arm design, prospective (n=15), retrospective (n=21) or not specified (n=2). Among 17 papers included for Key Question 3, five were randomized controlled trials (RCTs), one was a nonrandomized comparative study and 11 were single-arm studies.

Grey Literature (Publication Bias)

Following 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 RCT that met the criteria for inclusion based on our protocol. This study (NCT00020709) is a phase 3 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. After a MEDLINE search of the NCT number and title, we did not find any published results; it is unknown if any data have been reported. In examination of the U.S. Food and Drug Administration website and the Scientific Information Packets received from device manufacturers, we identified no additional RCTs that were relevant to this CER.

Figure 4. PRISMA diagram for identified trials



^aThree studies addressed both Key Questions 1 and 2.

^bOverlapping patient population refers to the studies in which the same patients were included in more than one study. In all such cases, only one study was included to avoid over sampling. Decision to include a study was based on the 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 Nonsurgical Interventions for Stage I NSCLC in Medically Inoperable Patients

Description of Included Studies

Table 2 provides a summary of characteristics of 35 single-arm studies that met our selection criteria for Key Question 1. Fourteen studies were prospective.^{17,47,49-59} Interventions included SBRT (24 studies, total n=1665 patients),^{17,48,49,53,56-75} three-dimensional radiotherapy (3DRT) (7 studies, total n=240 patients),^{50,51,54,55,76-78} proton beam radiotherapy (PBRT) (three studies,

total n=144 patients)^{47,52,79} and radiofrequency ablation (RFA) (1 study, n=19 patients).⁸⁰ More detailed information on the interventions is provided in Appendix C. Patients included in these studies were typically in their 70s, with median ages ranging from 67-81 years, and an overall range from 31-93 years. Common reasons for medical inoperability included presence of pulmonary disease (chronic obstructive pulmonary disease), insufficient predicted post-therapy 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,^{51,52,54,56,60,61,63-66,71,74} Eastern Cooperative Oncology Group (ECOG),^{50,57,69,70,72,74,76,77} World Health Organization (WHO)^{48,49,53,75}, or European Organization for Research and Treatment of Cancer (EORTC)⁷⁹ KPS ranged from 0-3 across 11 studies. Performance status was not reported in 11 studies.^{17,47,55,58,59,62,67,68,73,78,80} Sixteen studies (46 percent) reported histological confirmation of NSCLC cell types in 100 percent of patients.^{47,49,50,52-54,56,60,61,66,67,71,76-78} The remaining nineteen (54 percent) studies^{17,48,54,56-58,61-64,67-69,71-75,79,80} included patients without histological confirmation of NSCLC. In 18 of such studies, a median 26 percent of patients did not have histologically confirmed NSCLC. Such studies used the rate of tumor growth in successive computed tomography (CT) scans and presence of 18F-fluorodeoxyglucose activity as a diagnostic marker of NSCLC rather than histological confirmation of NSCLC.

Key Points

- All evidence included in this report for Key Question 1 is from single-arm studies. No evidence is available from any type of direct comparative study of one intervention versus another.
- Evidence compiled from 35 single-arm studies is insufficient to form conclusions about the comparative benefits or harms of SBRT (24 studies), 3DRT (seven studies), PBRT (three studies) and RFA (one study) in medically inoperable patients with stage I NSCLC.
- The evidence comprises direct outcomes overall survival and cancer-specific survival; an indirect outcome, local control; and radiation-associated toxicities.
- Overall, post-treatment toxicities were reported across studies, but no relative trend was detected among interventions.
- We are uncertain whether the limited evidence on adverse events (AEs) reflects their absence, or that the investigators did not systematically collect those data or report them.

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

| Treatment | Author, Year, Country | Design (Quality) ⁴² | Number of Patients | Intervention Details | 100% Histopathology Confirmation (% Not Confirmed) | Age, Years | % Female |
|-----------|--|--------------------------------|---|---|--|----------------------------|----------|
| 3DRT | Bogart et al, 2010, USA ⁵⁰ | Prospective (Poor) | 39 | 70 Gy 17-29 frs | Yes | 75 (48-87) | 53% |
| | Bradley et al, 2003, USA ⁵¹ | Prospective (Fair) | 56 | 70 Gy 5 frs | Yes | 73 (52-90) | 57% |
| | Campeau et al, 2009, Australia ⁷⁶ | Retrospective (Fair) | 34 | 60 Gy 30 frs | Yes | 81 (54-88) | 41% |
| | Graham et al, 2006, Australia ⁷⁷ | Retrospective (Fair) | Total: 39 (100%) Medically inoperable: 36 (92%) Refused surgery or NR: 3 (8%) | 65 Gy 35 frs Concurrent end-phase boost | Yes | 72 ^B (53-84) | 38% |
| | Jimenez et al, 2010, Spain ⁷⁸ | Retrospective (Poor) | 47 | 79Gy 44 frs (calculated) | Yes | 68±10 | 23% |
| | Mirri et al, 2009, Italy ⁵⁴ | Prospective (Poor) | 15 | 40 Gy BED: 72 Gy 5 frs | No (27%) | 76 ^B | NR |
| | Narayan et al, 2004, USA ⁵⁵ | Prospective (Poor) | 13 | 92 or 103 Gy 44-49 frs (calculated) | Yes | 67±18 | 9% |
| PBRT | Bush et al, 2004, USA ⁵² | Prospective (Good) | Total: 68 (100%) Medically inoperable: 63 (93%) Refused surgery: 5 (7%) | 51 CGE 10 frs 60 CGE 10 frs | Yes | 72 (52-87) | 56% |
| | Iwata et al, 2010, Japan ⁴⁷ | Prospective (Good) | Total: 57 (100%) Medically inoperable: 29 (51%) Refused surgery: 28 (49%) | 80 or 60 Gy BED: 96- 112 Gy 20 frs | Yes | 76 (48-89) | 29% |
| | Nakayama et al, 2010, Japan ⁷⁹ | Retrospective (Poor) | Total: 55 (100%) Medically inoperable: 52 (94%) Refused surgery: 3 (6%) | 66-73 GyE, 10-22 frs | No (12%) | 74±9 | 26% |
| RFA | Pennathur et al, 2007, USA ⁸⁰ | 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% |

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

| Treatment | Author, Year, Country | Design (Quality) ⁴² | Number of Patients | Intervention Details | 100% Histopathology Confirmation (% Not Confirmed) | Age, Years | % Female |
|--------------------------------------|--|---|---|---------------------------------------|--|-------------------------|----------|
| SBRT | Andratschke et al, 2011, Germany ⁶⁰ | Retrospective (Poor) | 92 | 24-45 Gy 3-5 frs | Yes | 75 (53-93) | 30% |
| | Baumann et al, 2006, Denmark ⁶² | Retrospective (Poor) | Total: 141 (100%) Medically inoperable: 136 (96%) Refused surgery: 5 (4%) | 30-48 Gy 2-4 frs | No (24%) | 74 (56-90) | 51% |
| | Baumann et al, 2009, Denmark ⁶¹ | Retrospective (Good) | Total: 57 (100%) Medically inoperable: 56 (99%) Refused surgery: 1 (2%) | 45 Gy BED: 112 Gy | No (33%) | 75 (59-87) | 54% |
| | Bollineni et al, 2012, Netherlands ⁷⁵ | Retrospective (Poor) | 132 | 60 Gy 3-8 frs | No (70%) | 75 (46-90) | 28% |
| | Burdick et al, 2010, USA ⁶³ | Retrospective (Fair) | 72 | 50-60 Gy 3-10 frs | No (32%) | 73 (52-90) | NR |
| | Coon et al, 2008, USA ⁶⁴ | Retrospective (Poor) | Total: 26 (100%) Medically inoperable: 24 (92%) Refused surgery: 2 (8%) | 60 Gy 3 frs | No (38%) | 76.5 ^a | NR |
| | Dunlap et al, 2010, USA ⁶⁵ | Retrospective (Fair) | Total: 40 (100%) Medically inoperable: 37 (92%) Refused surgery: 3 (8%) | 30-60 Gy BED: 78-180 Gy 3-5 frs | Yes | 73 (54-87) | NR |
| | Fritz et al, 2008, Germany ⁶⁶ | Retrospective (Fair) | Total: 40 (100%) Medically inoperable: 37 (92%) Refused surgery: 3 (8%) | BED: 100 Gy | Yes | 74 (59-82) | 20% |
| | Kopek et al, 2009, Denmark ⁵³ | Prospective (Good) | 88 | 45 or 68 Gy 3 frs | Yes | 73 (47-88) | 49% |
| | Nyman et al, 2006, Sweden, ⁵⁶ | Prospective (Fair) | 45 | 45 Gy 3 frs | No (20%) | 74 ^b (58-84) | 44% |
| Olsen et al, 2011, USA ⁶⁷ | Retrospective (Poor) | Total: 130 (100%) Medically inoperable: 117 (90%) Refused surgery: 13 (10%) | 45-54 Gy 3-5 frs | No (15%) | 75 (31-92) | 50% | |

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

| Treatment | Author, Year, Country | Design (Quality) ⁴² | Number of Patients | Intervention Details | 100% Histopathology Confirmation (% Not Confirmed) | Age, Years | % Female |
|------------------|--|--------------------------------|---|---------------------------------------|--|-------------------------|----------|
| SBRT (continued) | Palma et al, 2011, Netherlands ¹⁷ | Prospective (Poor) | Total: 176 (100%) Medically inoperable: 169 (96%) Refused surgery or NR: 7 (4%) | 54-64 Gy 3-8 frs | No (68%) | 70 (47-86) | 45% |
| | Pennathur et al, 2009, USA ⁶⁸ | Retrospective (Fair) | 21 | 20-60 Gy BED: 60-70 Gy 1-3 frs | No (5%) | 71 (61-85) | 57% |
| | Ricardi et al, 2010, Italy ⁵⁷ | Prospective (Poor) | Total: 62 (100%) Medically inoperable: 56 (90%) Refused surgery: 6 (10%) | 45 Gy BED: 124 Gy 3 frs | No (36%) | 74 ^p (53-83) | 16% |
| | Scorsetti et al, 2007, Italy ⁶⁹ | NR (Poor) | 43 | 20-32 Gy BED: 40-117 Gy 2-4 frs | No (5%) | 75 (52-90) | 21% |
| | Shibamoto et al, 2012, Japan ⁴⁹ | Prospective (Good) | Total: 180 (100%) Medically inoperable: 120 (67%) Refused surgery: 60 (33%) | 44-52 Gy 4 frs | Yes | 77 (29-89) | 32% |
| | Song et al, 2009, Korea ⁷⁰ | Prospective (Good) | Total: 32 (100%) Medically inoperable: 31 (97%) Refused surgery: 1 (3%) | 40-60 Gy 3-4 frs | Yes | 72 (58-89) | 19% |
| | Stephans et al, 2009, USA ⁷¹ | Retrospective (Good) | 86 | 50-60 Gy 3-5 frs | No (29%) | 73 (40-90) | 56% |
| | Takeda et al, 2009, Japan ⁴⁸ | Retrospective (Fair) | Total: 63 (100%) Medically inoperable: 49 (78%) Refused surgery: 14 (22%) | 50 Gy 5 frs | No (17%) | 78 (56-91) | 36% |
| | Taremi et al, 2011, Canada ⁵⁸ | Prospective (Fair) | 108 | 48-60 Gy 3-10 frs | No (29%) | 73 (48-90) | 51 |
| | Turzer et al, 2011, Norway ⁷² | Retrospective (Fair) | Total: 36 (100%) Medically inoperable: 35 (97%) Refused surgery: 1 (3%) | 45 Gy 3 frs | No (26%) | 74 (54-85) | 64% |

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

| Treatment | Author, Year, Country | Design (Quality) ⁴² | Number of Patients | Intervention Details | 100% Histopathology Confirmation (% Not Confirmed) | Age, Years | % Female |
|------------------|--|--------------------------------|---|----------------------|--|------------|----------|
| SBRT (continued) | 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, Netherlands ⁷³ | NR (Poor) | Total: 70 (100%) Medically inoperable: 65 (93%) Refused surgery: 5 (7%) | 36-60 Gy 3 frs | No (49%) | 76 (54-90) | NR |
| | Videtic et al, 2010, USA ⁷⁴ | 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 = gray; GyE = gray equivalent; NR = not reported; PBRT = proton beam radiotherapy; RFA = radiofrequency ablation; SBRT = stereotactic body radiotherapy

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

^aMedian.

^bMean.

Detailed Synthesis

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

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

| Intervention | Reported Overall Survival Rates, Number of Studies (Number of Patients) ^a | Reported Cancer-Specific Survival Rates, Number of Studies (Number of Patients) ^a | Reported Local Control Rates, Number of Studies (Number of Patients) ^a |
|--------------|---|--|--|
| 3DRT | 3-years: 33-61% 4 studies ^{51,54,55,78} (n=131) 5-years: 30% 1 study ⁷⁷ (n=36) | 3-years: 48%, 51% 2 studies ^{51,55} (n=69) 5-years: 53% 1 study ⁷⁷ (n=36) | 3-years: 63%, 72% 2 studies ^{51,54} (n=71) 5-years: NR |
| SBRT | 3-years: 52-77% 7 studies ^{48,49,57,61,62,66,74} (n=480) 5-years: 17-44% 6 studies ^{17,49,53,56,60,62} (n=650) | 3-years: 57-94% 6 studies ^{48,57,61,62,65,66} (n=371) 5-years ^{56,60,62} : 40-48% 3 studies ^{47,51,53} (n=273) | 3-years: 81-94% 5 studies ^{17,57,61,66,74} (n=344) 5-years: 83% 1 study ⁶⁰ (n=92) |
| PBRT | 3-years: 44%, 65% 2 studies ^{47,52} (n=92) | 3-years: 72% 1 study ⁵² (n=63) | 3-years: 74% 1 study ⁵² (n=63) |
| RFA | 2-years: 68% 1 study ⁸⁰ (n=19) | 83% at FU 1 study ⁸⁰ (n=19) | 58% at FU 1 study ⁸⁰ (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

^aNumber of patients represents only inoperable.

The evidence summarized in Table 3 reflects single-arm studies that report direct outcomes- overall survival and cancer-specific survival and an indirect outcome- local control. Rates for overall survival, cancer-specific survival, and local control for SBRT at 3-years followup suggest a possible trend toward exceeding those reported with 3DRT. However, the reported ranges overlap. Furthermore, as this evidence comprises single-arm studies with no direct comparisons, conclusions are precluded. The nature of the evidence – no RCTs- 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. The reported toxicities are grade 2 or greater (moderate) on a standardized criteria such as Common Toxicity Criteria for Adverse Events (CTCAE), or the WHO scale. They are all similar with respect to their grades and definitions. For Key Questions 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 nine (41 percent) SBRT studies^{17,53,56,57,60-62,65,66} and one PBRT study.⁷⁹ One death was attributed to grade 5 pericardial effusion at 3 months post-treatment in a 3DRT study.⁵⁴ A second death was attributed to grade 5 hemoptysis in an SBRT study.⁷⁰ Complications associated with RFA included pneumothorax and prolonged air leak from the lung.

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

Table 4. Percentage of studies reporting intervention-associated toxicities in stage I medically inoperable NSCLC patients

| Toxicity | SBRT n=24 Studies (%) | 3DRT n=7 Studies (%) | PBRT n=3 Studies (%) | RFA n=1 Study (%) |
|--------------|--------------------------|-------------------------|-------------------------|----------------------|
| None | 4 (17) | 2 (29) | 1 (33) | 0 |
| Grade 2 | 9 (38) | 3 (43) | 1 (33) | NA |
| Grade > 2 | 13 (54) | 2 (29) | 1 (33) | NA |
| Rib Fracture | 9 (38) | 0 | 1 (33) | NA |
| Mortality | 1 (4) | 0 | 1 (33) | 1 (100) |

3DRT = three dimensional radiotherapy; NA = not applicable; 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. We are uncertain whether the limited evidence on AEs reflects absence, or that the investigators did not systematically collect data or report them.

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

Description of Included Studies

Table 5 provides a summary of characteristics of six single-arm studies that address Key Question 2. Three studies were prospective.^{47,49,81} Three studies⁸¹⁻⁸³ used SBRT and enrolled only operable patients and two studies^{48,49} used SBRT and enrolled inoperable and operable patients but reported outcomes separately. One study⁴⁷ used PBRT. Overall, patients were typically in their mid-70s, with median ages ranging from 74⁸³ to 78⁴⁸ years, and overall range from 43-91 years. Sex distribution was uneven, with proportions of females ranging from 40 percent⁸¹ to 72 percent⁸³ across studies. ECOG and WHO performance status ranged from 0-3 across studies. Four studies reported 100 percent histological confirmation of NSCLC cell type.^{47,49,81,83} Details on the included studies are provided in Appendix C.

Key Points

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

- We are uncertain whether the limited evidence on AEs reflects absence, or that the investigators did not systematically collect data or report them

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

| Treatment | Author, Year, Country | Design (Quality) ⁴² | Number of Patients | Intervention Details | 100% Histopathology Confirmation (% Not Confirmed) | Age, Years (Range) ^a | % Female |
|-----------|---|--------------------------------|---|---|--|---------------------------------|----------|
| PBRT | Iwata et al, 2010, Japan ⁴⁷ | Prospective (Good) | Total: 57 (100%) Medically inoperable: 29 (51%) Refused surgery: 28 (49%) | 80 or 60 Gy BED: 96-112 Gy 20 frs | Yes | 76 (48-89) | 29% |
| SBRT | Chen et al, 2012, USA ⁸¹ | Prospective (Poor) | 40 | 50 Gy 3 frs | Yes | 76 (63-87) | 60% |
| SBRT | Lagerwaard et al, 2011, Netherlands ⁸² | Retrospective (Poor) | 177 | 60 Gy BED > 100 Gy for all frs 3, 5, or 8 frs | No (66%) | 76 (50-91) | 43% |
| SBRT | Onishi et al, 2011, Japan ⁸³ (longer FU to Onishi et. al, 2007) ⁸⁴ | Retrospective (Good) | 87 | 45-72 Gy BED:116 Gy (100-141) 3-10 frs | Yes | 74 (43-87) | 28% |
| SBRT | Shibamoto et al, 2012, Japan ⁴⁹ | Prospective (Good) | Total: 180 (100%) Medically inoperable: 120 (67%) Refused surgery: 60 (33%) | 44-52 Gy 4 frs | Yes | 77 (29-89) | 32% |
| SBRT | Takeda et al, 2009, Japan ⁴⁸ | Retrospective (Fair) | Total: 63 (100%) Medically inoperable: 49(78%) Refused surgery: 14 (22%) | 50 Gy 5 frs | No (18%) | 78 (56-91) | 36% |

BED = biologically effective dose; frs = fractions; FU = followup; Gy = gray; NR = not reported; PBRT = proton beam radiotherapy; SBRT = stereotactic body radiotherapy

^aValues are median (range).

Detailed Synthesis

Appendix C shows survival and local control outcomes with PBRT or SBRT in four studies relevant to Key Question 2. Survival outcomes were not reported in these the studies. Table 6 shows survival and local control outcomes for each intervention.

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

| Intervention | Reported Overall Survival Rates, Number of Studies (Number of Patients) ^a | Reported Cancer-Specific Survival Rates, Number of Studies (Number of Patients) ^a | Reported Local Control Rates, Number of Studies (Number of Patients) ^a |
|--------------|--|--|--|
| PBRT | 3-years: 80% 1 study ⁴⁷ (n=28) | NR | NR |
| SBRT | 3-years: 74%- 91% 4 studies ^{48,49,81,82} (n=291) 5-years: 70%, 70% 2 studies ^{49,83} (n= 87) | 3-years: 91% 1 study ⁴⁸ (n=14) 5-years: 76% 1 study ⁸³ (n=87) | 3-years: 93% 1 study ⁸² (n=177) 5-years: 87% 1 study ⁸³ (n= 87) |

NR = not reported; NSCLC = non-small-cell lung cancer; PBRT = proton beam radiotherapy; SBRT = stereotactic body radiotherapy

^aNumber of patients who were operable but refused surgery.

The evidence summarized in Table 6 above comprises single-arm studies that report direct outcomes overall survival and cancer-specific survival and an indirect outcome, local control. No direct comparative evidence is available to suggest any relative difference between the technologies in overall survival, cancer-specific survival 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 two (67 percent) SBRT studies^{82,83} and in the PBRT study.⁴⁷ 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. Percentage of studies reporting intervention-associated toxicities in stage I medically operable NSCLC patients

| Toxicity | SBRT n=5 Studies (%) | PBRT n=1 Study (%) |
|--------------|-------------------------|-----------------------|
| None | 2 (40) | 0 |
| Grade 2 | 2 (40) | 1 (100) |
| Grade > 2 | 3 (60) | 1 (100) |
| Rib Fracture | 2 (40) | 1 (100) |
| Other | NR | NR |

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

No relative trend in reporting toxicities was discerned among interventions. We are uncertain whether the limited evidence on AEs reflects absence, or that the investigators did not systematically collect data or report them.

Risk of Bias for Individual Studies Addressing Key Question 1 and Key Question 2

We used the convention described by Carey and Boden⁴² to assess the risk of bias of individual single-arm studies included to address Key Question 1 and Key Question 2 (see

Methods chapter). Our ratings of good, fair and poor are shown in Table 8. Studies that met 8 of 8 criteria were classified as good, studies that met 7 of 8 criteria were classified as fair and studies that met fewer than 7 criteria were classified as poor.

Among 38 unique single-arm studies, all reported the use of validated outcomes. Study quality was most often downgraded because authors did not acknowledge the funding source in 23 studies (60 percent).^{48,51,54,56,57,59,62-69,72-74,76-79,81,82} In eleven studies (29 percent)^{17,54,55,57,59,60,67,75,78,79,81} it was unclear whether or not the conclusions and discussion were supported by the data. Eight studies (23 percent)^{17,50,54,55,58,59,67,73} did not adequately describe the study population. Six (16 percent)^{54,55,59,78,79,81} did not describe results well. Four (10 percent)^{50,75,79,82} did not adequately describe the intervention. Three (9 percent)^{54,60,64} did not report the use of appropriate statistical analysis. The only consistent reason for which a study was downgraded was “failure to report the funding source.”

Table 8. Carey and Boden study quality rating summaries for Key Questions 1 and 2

| Key Question (Number of Unique Studies) | Good (8 of 8 “Yes”) | Fair (7 of 8 “Yes”) | Poor (< 7 of 8 “Yes”) |
|--|--------------------------------------|---|--|
| Key Question 1 (n=35) | 8 ^{47,49,52,53,61,70,71,80} | 12 ^{48,51,56,58,63,65,66,68,72,74,76,77} | 15 ^{17,50,54,55,57,59,60,62,64,67,69,73,75,78,79} |
| Key Question 2 (n=3) | 1 ⁸³ | 0 | 2 ^{81,82} |
| Total | 9 (24%) | 12 (32%) | 17 (44%) |

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

Overview

This section describes the literature that evaluates the efficacy and safety of local nonsurgical 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 as both median overall survival and time specific survival), 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.

Overall, 17 studies were abstracted for this review. The evidence base consisted of six comparative studies⁸⁵⁻⁹⁰ and 11 noncomparative studies.⁹¹⁻¹⁰¹ 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 Key Question 3, five were RCTs and one was a retrospective nonrandomized comparative study. Three hundred and forty-two patients

were randomized in these six studies⁸⁵⁻⁹⁰ that compared six distinct treatment combinations. Additionally, we did not report data for one RCT¹⁰² as it reported outcome data for three different endobronchial treatments cumulatively. The detailed outcomes related to symptom improvement, survival and AEs for all six comparative studies are presented in Appendix C. All six studies included patients with a histologically confirmed NSCLC. Four studies^{85,86,89,90} reported staging of lung cancer patients but only one study⁸⁶ reported the criteria used for staging NSCLC. The duration of the study enrollment period was reported by four studies^{85,87,88,90} and ranged from 2 to 4 years. Three studies^{85,87,88} were conducted in an outpatient setting; one⁹⁰ was conducted in the inpatient setting and for two studies^{86,89} study setting was not reported. Four^{85,88-90} were single-center studies, the remaining two^{86,87} were multicenter studies. Four studies⁸⁷⁻⁹⁰ did not state whether there existed a conflict of interest or not, the remaining two studies^{85,86} stated no conflict of interest. Three studies^{87,88,90} did not state the source of funding, one each was manufacturer sponsored,⁸⁹ professional scientific society sponsored⁸⁶ and investigator initiated.⁸⁵

All six⁸⁵⁻⁹⁰ comparative studies were rated as poor quality, five studies^{85-88,90} reported data on symptom relief, five studies^{85-88,90} reported survival data, two studies reported quality of life (QOL) data^{85,87} and six studies⁸⁵⁻⁹⁰ 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 that address Key Question 3

| Treatment | Author, Year, Country | Design | N | GQ | FQ | PQ | OS | DSS | LCT | SC | QOL | TOX | |
|--------------------------------|--|--------|-----|-----|----|----|----|-----|-----|----|-----|-----|---|
| BT + EBRT vs. BT alone | Mallick-2006, India ⁸⁵ | RCT | 45 | | | • | | | | • | • | • | |
| BT + EBRT vs. EBRT alone | Langendijk-2001, Netherlands ⁸⁶ | RCT | 98 | | | • | • | | | • | | • | |
| BT vs. EBRT | Stout-2000, UK ⁸⁷ | RCT | 108 | | | • | • | | | • | • | • | |
| Laser + BT vs. laser alone | Chella-2000, Italy ⁸⁸ | RCT | 29 | | | • | • | | | • | | • | |
| Laser vs. photodynamic therapy | Jimenez-1999, Spain ⁸⁹ | RCT | 31 | | | • | • | | | | | • | |
| Laser vs. Electrocautery | van Boxem-1999, Netherlands ⁹⁰ | NRC | 31 | | | • | • | | | • | | • | |
| | Overall | | 6 | 342 | 0 | 0 | 6 | 5 | 0 | 0 | 5 | 2 | 6 |

BT = 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 of poor quality according to the U.S. Preventive Services Task Force (USPSTF) rating criteria.
- Evidence from six comparative studies is insufficient to draw conclusions about relative benefits and harms of six unique treatment comparisons (brachytherapy plus external-beam radiotherapy (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 (PDT) for local nonsurgical therapies in symptomatic inoperable patients with obstructive endoluminal NSCLC.

- None of the six comparative studies included interventions related to debridement and stenting and RFA. These interventions are addressed in three single-arm studies.
- The evidence comprises direct outcomes (overall survival), 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 underreporting of treatment-related toxicities, as three comparative studies did not describe the frequency, process of data collection, or assessment of severity of treatment-related toxicities.

Table 10. Study characteristics of comparative studies that address Key Question 3

| Treatment | Author, Year, Country | N | Stage Distribution | Histopathology Confirmation | Age, Years ^a | Females | PS |
|----------------------------|--|---|--|-----------------------------|---------------------------------------|--|--|
| BT + EBRT vs. BT alone | Mallick-2006, India ⁸⁵ (RCT) | N: 45 (100%) EBRT+BT-16Gy: 15 (33.3%) EBRT+BT-10Gy: 15 (33.3%) BT-15Gy: 15 (33.4%) | III: 45 (100%) | Yes | 64.5 (35-75) | Total: 2 (4%) | NR |
| BT + EBRT vs. EBRT alone | Langendjik-2001, Netherlands ⁸⁶ (RCT) | N: 95 (100%) EBRT+BT: 47 (49%) EBRT: 48 (51%) | EBRT +BT vs. EBRT I: 4 (9%) vs. 5 (10%) III: 43 (91%) vs. 43 (90%) | Yes | EBRT+BT: 67 (±9) EBRT: 68 (±9) | EBRT+BT: 9 (19%) EBRT: 8 (17%) | NR |
| BT vs. EBRT | Stout-2000, UK ⁸⁷ (RCT) | N: 108 (100%) BT: 49 (49%) EBRT: 50 (51%) | NR | Yes | 68 ^b (40-84) | 20 (20%) | NR |
| Laser + BT vs. laser alone | Chella-2000, Italy ⁸⁸ (RCT) | N: 29 (100%) YAGL+BT: 14 (48%) YAGL: 15 (52%) | NR | Yes | 61 ^b (47-76) | 6 (21%) | WHO 0: 3 (10%) I: 11 (40%) II: 15 (52%) |
| Laser vs. PDT | Jimenez-1999, Spain ⁸⁹ (RCT) | N: 31 (100%) PDT: 14 (45%) YAGL: 17 (55%) | PDT 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 ⁹⁰ (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 |

BT = brachytherapy; EBRT = external beam radiotherapy; ECAU = electrocautery; Gy = gray; N = total sample size of the study; NR = not reported; NRC = nonrandomized comparative study; PDT = photodynamic therapy; PS = performance status; R = recurrent; RCT = randomized controlled trial; WHO = World Health Organization;

YAGL = yttrium aluminum garnet laser

^aValues are mean (±SD) or median (range) unless specified.

^bMean (range).

Description of Comparative Studies According to Intervention(s)

Brachytherapy Plus EBRT Versus Brachytherapy Alone

One RCT⁸⁵ compared brachytherapy plus EBRT versus brachytherapy alone and included a total of 45 patients (Table 11 and 12). These 45 patients were randomized equally across three treatment groups; EBRT plus brachytherapy (16 Grays [Gy]), 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 periods (at weekly intervals for acute toxicities) using a standardized Radiation Therapy Oncology Group (RTOG) morbidity-scoring criterion. This was the strength of this trial. Weaknesses of the trial included lack of sample size calculation, small number of patients per treatment group, and lack of defined statistical adjustments for multiple comparisons. These weaknesses affected the USPSTF domain of “appropriate analysis of results” (Table 13). Further, no details were provided on randomization or allocation concealment, which adversely affected the USPSTF domain of “assembled comparable groups.” Therefore, we judged this trial to have a poor USPSTF quality rating.

There was no statistical difference in the response rate of dyspnea, cough, hemoptysis and obstructive pneumonia among the 3 treatment groups. 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 trial⁸⁵

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

BT = brachytherapy; EBRT = external beam radiotherapy; Gy = gray; n = number; Rx = treatment

*Represents number of patient who had complete or partial response.

Note: There were no statistically significant differences between any treatment arms.

Table 12. Comparative effect of brachytherapy plus EBRT versus brachytherapy alone on quality of life outcomes in the Mallick trial⁸⁵

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

BT = 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 trial⁸⁵

| 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 RCT⁸⁶ compared brachytherapy plus EBRT versus EBRT alone. The trial 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 (Table 14). However, the trial 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. The USPSTF trial quality rating was poor (Table 15). The analysis with 95 patients was underpowered to detect a prespecified difference in the rate of dyspnea (a primary outcome) and therefore adversely affected 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 affected 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% confidence interval (CI): 5.3 to 8.9) and 8.5 (95% CI: 5.4 to 11.6) months respectively. The authors assessed QOL scores (Dutch version of the EORTC Quality of Life Questionnaire (EORTC QLQ-C30) and lung cancer module QLQ-LC13) both before and after therapy with a 90 percent compliance rate, but the results were not reported in the paper. 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 Langendijk trial⁸⁶

| Treatment Groups | Dyspnea | Cough | Hemoptysis | Others |
|------------------------|-------------------------|----------|------------|--|
| EBRT + BT (% 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% |

BT = brachytherapy; EBRT = external beam radiotherapy; NS = nonsignificant

Table 15. USPSTF study quality ratings of the Langendijk trial⁸⁶

| 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 controlled trial⁸⁷ randomly allocated 108 inoperable NSCLC patients with endobronchial tumors to two treatment arms: brachytherapy (n=49) or EBRT (n=50) (Table 16). Nine patients

were excluded from the analysis. The primary aim of the trial was to evaluate symptom relief, treatment-related toxicities and impact on QOL. The strength of the trial was that it assessed treatment harms adequately at predefined periods using patient questionnaires but did not use standardized scoring criteria to rate severity of treatment-related toxicities. The trial 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 negatively affected all three domains of USPSTF quality rating: “maintained comparable groups,” “measurements valid” and “appropriate analysis of results” (Table 17) Further, lack of details about randomization and allocation concealment adversely affected 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 trial⁸⁷

| Treatment Groups | Time | Dyspnea | Hemoptysis | Breathlessness |
|--|---------|------------|------------|----------------|
| BT (% 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) |

BT = 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 trial⁸⁷

| 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 RCT¹⁰² randomly allocated patients to EBRT or endobronchial treatment (clinician choice of any one endobronchial treatment: brachytherapy, laser therapy or cryotherapy). This trial 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 four treatment arms. The trial¹⁰² 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 trial in this report. Details of this trial are provided in the abstraction tables in Appendix C.

Laser Plus Brachytherapy Versus Laser Alone

One RCT⁸⁸ compares combination treatment of laser plus brachytherapy versus laser therapy only (Table 18). This trial by Chella et al.,⁸⁸ randomized 29 patients across two treatment arms: laser plus brachytherapy (n=14) versus laser (n=15) alone. This small trial lacked details on randomization and 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 affected the USPSTF domain of “measurements valid” (Table 19) We therefore rated this trial 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 arms (10.3 months and 7.4 months respectively). Speiser’s index (a semi-quantitative score in which a higher score indicates severe obstruction) was reduced by 4.2 and 3.4 points in the combined versus single treatment arms respectively. This reduction in score was not statistically different between the two arms. The authors also reported the pretreatment and post-treatment values of lung function tests but showed no statistically significant differences between the treatment arms. One patient died due to hemoptysis 12 months after treatment in the laser plus brachytherapy arm.

Table 18. Comparative effect of laser plus brachytherapy versus laser alone on obstructive symptoms in the Chella trial⁸⁸

| 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 trial

Table 19. USPSTF study quality ratings of the Chella trial⁸⁸

| 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 controlled trial⁸⁹ randomized 31 NSCLC patients with airway obstruction to either PDT (n=14) versus laser therapy (n=17). The trial assessed treatment harms at predefined and regular periods and assessed causality but the authors did not report using standardized criteria to assess the severity of treatment-related toxicities. This small trial lacked details on randomization and allocation concealment. At the baseline, the proportion of patients with stage III–IV cancer in the PDT 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 trial.

Further, the authors did not report whether they adjusted for the baseline differences in the outcomes. This negatively affected the USPSTF domain of “assembled comparable groups” and was considered a fatal flaw in the USPSTF quality rating (Table 20). We therefore judged this trial to have a poor USPSTF quality rating.

Median survival was reported to be longer in the PDT 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, and there was one probable death due to treatment in the PDT-treated group.

Table 20. USPSTF study quality ratings of the Jimenez trial⁸⁹

| 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 study⁹⁰ 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” (Table 21).

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 study⁹⁰

| 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

A total of 11 studies⁹¹⁻¹⁰¹ included 858 patients given eight distinct treatment modalities (three single intervention: brachytherapy, PDT, RFA; five multiple interventions: brachytherapy plus EBRT, brachytherapy plus PDT plus chemotherapy, EBRT plus chemotherapy, stenting plus brachytherapy and stenting plus laser therapy). Data were abstracted from a single arm of three otherwise comparative studies.^{91,93,96} In the latter, the comparator arms were not considered

relevant and not abstracted, for reasons summarized in the section, “Description of Noncomparative Studies” below. Three studies (27 percent) originated in the United States, seven were from Europe (64 percent), and one (9 percent) was from former Yugoslavia. An overview of the noncomparative studies is given in Table 22.

Table 22. Overview of noncomparative studies of local nonsurgical endobronchial therapies

| Treatment | Author, Year | Time | N | OS | DSS | LCT | SC | QOL | TOX |
|-----------------|---|------|-----|----|-----|-----|----|-----|-----|
| BT | Celebioglu-2002, Turkey ⁹⁴ | R | 95 | | | | • | | • |
| BT | Guilcher-2011, France ⁹⁵ | R | 226 | • | • | • | | | • |
| BT | Petera-2001, Czech Republic ⁹⁶ | NR | 41 | • | | | • | | |
| PDT | Jones-2001, USA ⁹⁷ | R | 10 | • | | | | | |
| RFA | Lencioni-2008, Multiple Countries ⁹¹ | P | 33 | • | • | | | • | • |
| BT + EBRT | Muto-2000, Italy ⁹⁸ | P | 320 | • | | | • | | |
| BT + EBRT | Vucicevic-1999, Yugoslavia ⁹⁹ | R | 39 | • | | | • | | • |
| BT + STNT | Allison-2004, USA ⁹² | P | 10 | • | | • | | • | |
| LASR + STNT | Chhajed-2006, Switzerland ⁹³ | R | 52 | | | | | | • |
| EBRT + CHEM | Celikoglu-2006, Turkey ¹⁰⁰ | P | 23 | | | | • | | |
| BT + CHEM + PDT | Weinberg-2010, USA ¹⁰¹ | 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

Key Points

- Of the total 11 noncomparative studies that addressed Key Question 3, we focused on three studies that cover two unique interventions (RFA and debriement and stenting) for which comparative data was not available.
- These three noncomparative studies included 95 patients, two studies were prospective^{91,92} and one was retrospective.⁹³
- All three non-comparative studies were of poor quality according to Carey and Boden quality ratings.
- The evidence comprises of overall survival reported by all three studies, lung function tests and QOL by one study⁹¹, performance status by one study⁹² and treatment-related toxicities by two studies.^{91,93}

Description of Noncomparative Studies

We do not present detailed study data (study characteristics and outcomes) of eight⁹⁴⁻¹⁰⁰ noncomparative studies that utilize interventions for which comparative studies exists. These interventions include brachytherapy, EBRT, laser, electrocautery and PDT. Instead, we focused on three noncomparative studies⁹¹⁻⁹³ that cover two unique interventions (RFA and debriement and stenting) for which comparative data was not available. Table 23 provides a summary of patient characteristics of three single-arm studies that covers RFA and debriement and stenting. It includes two studies on combination treatment with stenting and one study on RFA.

Among these three noncomparative studies, two were prospective^{91,92} and one was retrospective.⁹³ Ninety-five patients were included in these three studies. The Lencioni and Chhajed studies included patients which were not relevant to Key Question 3. The Lencioni study included 73 patients with non-NSCLC malignancy; the Chhajed study included 92 NSCLC patients that did not have endobronchial obstruction and received chemotherapy. The data

presented in this report for these two studies exclude data of such non-relevant patient population. All but one study⁹³ included patients with a histologically non-confirmed NSCLC. One study⁹² included only recurrent patients, one study⁹¹ included recurrent and stage I patient, and the third study⁹³ did not report on tumor stage of patients. None of the three studies reported the criteria used for staging NSCLC. The duration of the study enrollment period was reported by only one study.⁹¹ One study⁹² was conducted in an outpatient setting; the remaining two studies^{91,93} did not describe the study setting. Two^{92,93} were single-center studies, the third⁹¹ was a multicenter study. All three studies⁹¹⁻⁹³ stated no conflict of interest. Two studies^{92,93} did not state the source of funding, the remaining study⁹¹ was manufacturer sponsored. All three noncomparative studies were rated as poor quality. All three studies reported data on survival data. The Lencioni study⁹¹ reported 1 and 2-year survival rates; Chhajed⁹³ reported 3, 9, and 12-month survival rates and median survival. However, of the 52 patients assessed in the Chhajed study, 13 each received laser and stenting alone respectively and remaining 26 patients received both laser and stenting. However, the authors did not present data of patients stratified by the treatment they received. This severely limited meaningful interpretation of the data. Mean survival for 10 patients included in the Allison study⁹² was not reported in the published paper but calculated for this report. Among the miscellaneous outcomes related to symptom relief and quality of life, the Lencioni study⁹¹ reported results of lung function tests and QOL and the Allison study⁹² reported results on performance status. The detailed outcomes related to survival, symptom improvement and quality of life are presented in Table 24.

Table 23. Study characteristics of noncomparative studies that address Key Question 3

| Treatment | Author, Year, Country | Design (Quality) ⁴² | N | Intervention Details | 100% Histopathology Confirmation (% Not Confirmed) | Age, Years ^a | % Female |
|-------------|---|--------------------------------|----|--|--|-------------------------|----------|
| RFA | Lencioni-2008, Multiple Countries ⁹¹ | Prospective (Poor) | 33 | Ablation protocol to destroy visible tumor mass plus 0.5 cm safety of margin | Yes | 67 (29-82) | 24% |
| BT + STNT | Allison-2004, USA ⁹² | Prospective (Poor) | 10 | 18Gy 3frs | Yes | 66.5 (52-77) | 20% |
| LASR + STNT | Chhajed-2006, Switzerland ⁹³ | Retrospective (Poor) | 52 | Laser ablation through a rigid bronchoscope, stenting when significant airway obstruction (>50%) | No (17%) | 61 ^b | 27% |

BT = brachytherapy; frs = fractions; Gy = gray; N = total sample size of the study; RFA = radiofrequency ablation; STNT = stenting; LASR = laser

^aValues are median (range) unless specified.

^bMean.

Table 24. Survival and local control outcomes for noncomparative studies that address Key Question 3

| Intervention | Author, Year | Reported Overall Survival Rates (Number of Patients) | Reported Cancer-Specific Survival Rates (Number of Patients) | Miscellaneous Outcomes |
|--------------|---------------------------------------|--|---|---|
| RFA | Lencioni-2008 (n=33) ⁹¹ | 1 yr: 70% (95% CI: 51 to 83) 2 yr: 48% (95% CI: 30 to 65) | 1 yr: 92% (95% CI: 78–98) 2 yr: 73% (95% CI: 54–86) | Lung function: (n=22) FEV, L 0 months: 1.9 (±0.9) 12 months: 1.5 (±0.7) FACT-G 0 months: 80.5 (±11.2) 12 months: 82.2 (±11.1) |
| BT + STNT | Allison-2004 (n=10) ⁹² | 10.3 months (±4.1) (calculated) | NA | Baseline KPS: 45 (±7.1) Post Rx KPS: 77 (±9.5) |
| LASR + STNT | Chhaged-2006 (n=52) ⁹³ | Median survival : 8.4 months (4.8-17.1) 3-months survival: 90% 6-months survival: 71% 12-months survival: 40% | NA | NR |

BT = brachytherapy; CI = confidence interval; FACT-G = Functional Assessment of Cancer Therapy- General; FEV = forced expiratory volume; frs = fractions; Gy = gray; KPS = Karnofsky performance status; L = liter; LASR = laser; N = total sample size of the study; NR = not reported; RFA = radiofrequency ablation; Rx = treatment; STNT = stenting

Intervention-Associated Adverse Events

As per Agency for Healthcare Research and Quality (AHRQ) guidance on comparing harms about medical interventions,¹⁰³ 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 AEs than the general population.¹⁰³ Therefore, we report the treatment-related toxicities data from all 11 noncomparative studies. These data are compiled in Table 25. In the largest prospective study⁹⁸ of 320 patients who were treated with a combination of brachytherapy and EBRT, radiation bronchitis was the most common treatment-related toxicity 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,⁹⁵ 226 patients with endobronchial NSCLC treated with brachytherapy 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 complications or not. There was only one study⁹¹ 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 four studies^{93,95,98,99} 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 25. Treatment-related toxicities in noncomparative studies that address Key Question 3

| Treatment | Author, Year | Hemoptysis | Pneumothorax | Radiation Bronchitis | Death | Others |
|-----------------|--------------------------------------|------------|----------------------|---|--|---|
| BT | Muto-2000 (N=320) ⁹⁸ | 10 (4%) | - | Grade 2: 20 (7%) Grade 3: 28 (10%) Grade 4: 23 (8%) | - | Bronchoesophageal fistulas: 3 (1%) |
| BT | Celebioglu-2002 (N=95) ⁹⁴ | | 0 | - | | Fistula: 0 Cardiovascular problems: 0 |
| BT | Guilcher-2011 (N=226) ⁹⁵ | 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) ⁹¹ | - | 5 (13%) ^a | - | - | |
| BT + EBRT | Vucicevic-1999 (N=39) ⁹⁹ | 1/39 (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) ⁹³ | 1 (2%) | - | - | Death within 24 h of the procedure: 1 (2%) | Stent migration: 3 (6%) Mucous plugging of the airway stent: 2 (4%) |
| BT + CHEM + PDT | Weinberg-2010 (N=9) ¹⁰¹ | - | - | - | - | Bronchial contraction: 5/9 (56%) Occlusion from bronchial contraction: 2/9 (22%) Photosensitivity: 2/9 (22%) |

BT = 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; PDT = photodynamic therapy;

RFA = radiofrequency ablation; STNT = stenting

^aThis is procedure level and not patient data. Forty procedures were done in 33 patients and 5 procedures were associated with pneumothorax.

Risk of Bias for Noncomparative Studies Addressing Key Question 3

We used the convention described by Carey and Boden⁴² to assess the risk of bias of individual noncomparative studies included to address Key Question 3 (see Methods chapter). We rated the quality of only three noncomparative studies that utilize interventions for which no comparative data was available. Our ratings of good, fair and poor are shown in Table 26. Studies that met 8 of 8 criteria were classified as good, studies that met 7 of 8 criteria were classified as fair and studies that met fewer than 7 criteria were classified as poor.

The reasons for not fulfilling Carey and Boden criteria were as follows: the Chhajed study⁹³ did not clearly define a research question, did not well describe the study population or the intervention used in the study nor did they describe the results well. One study⁹¹ did not use validated outcome measure, two studies^{91,92} did not use appropriate statistical analysis, discussion and conclusion was not supported by data for two studies^{91,93} and two studies^{92,93} did not describe their funding source.

Table 26. Carey and Boden quality rating summary

| Key Question (Number of Studies) | Good (8 of 8 "Yes") | Fair (7 of 8 "Yes") | Poor (< 7 of 8 "Yes") |
|---|--------------------------------|--------------------------------|--|
| Key Question 3 (3) | 0 | 0 | 3 |
| Total | 0 | 0 | 3 (100%) |

Discussion

Overview

This chapter presents a discussion of the results of the comparative effectiveness review (CER) organized as follows:

- Key Findings
- Strength of Evidence (SOE)
- Relationship of the Findings to Existing Information
- Applicability of the Findings
- Implications for Clinical and Policy Decisionmaking
- Limitations of the CER Process
- Limitations of the Evidence Base
- Research Gaps and Conclusions
- In each of the above-mentioned sections, the results are organized by Key Questions 1, 2, and 3.

Key Findings

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

- Thirty-five 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, cancer-specific survival and local control rates. Harms were radiation-induced for 3DRT, PBRT and SBRT and procedural complications for RFA.
- No studies 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 Nonsurgical Interventions in Medically Operable Patients With Stage I NSCLC

- Six 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 overall survival, cancer-specific survival and local control rates. Harms were radiation-induced for PBRT and SBRT.
- No studies 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 Nonsurgical 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 nonsurgical therapies (external-beam radiotherapy (EBRT), brachytherapy, laser therapy, photodynamic therapy (PDT) and electrocautery) for palliation in symptomatic inoperable patients with obstructive endoluminal NSCLC. Reported clinical benefits included post-treatment symptom relief and overall survival. 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.
- Evidence from three single-arm studies of debriement and stenting is insufficient to draw conclusions about the effectiveness of those interventions.
- The evidence is insufficient to answer Key Question 3.

Strength of Evidence

To evaluate the SOE, we used an approach that was specifically developed for the Evidence-based Practice Center program and referenced in the Methods Guide.³⁷ This approach is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.⁴³ This system explicitly addresses four required domains: risk of bias, consistency, directness, and precision, as outlined in the Methods section.

Key Question 1

As shown in Table 27 below, the overall SOE is insufficient to form conclusions about the comparative beneficial effects or toxicities of 3DRT, PBRT, RFA or SBRT in the treatment of stage I NSCLC in medically inoperable patients. Direct outcomes of interest were overall survival, cancer-specific survival, and toxicities.

Thirty-five single-arm studies were available. The risk of bias among the studies was inherently high. The consistency of effect size direction cannot be determined in the absence of comparative studies, so this domain was deemed unknown. No direct comparative evidence is available among interventions, so this domain was deemed indirect. Because precision cannot be determined in the absence of direct comparative evidence among interventions, we deemed the evidence to be imprecise.

Table 27. Strength of evidence for local nonsurgical interventions in medically inoperable stage I NSCLC patients

| Treatment and Evidence Base | Risk of Bias | Consistency | Directness | Precision | Overall Strength of Evidence |
|--|--------------|-------------|------------|-----------|------------------------------|
| SBRT (22 single-arm studies, ^{17,48,49,53,56-75} total n=1665 patients) | High | Unknown | Indirect | Imprecise | Insufficient |
| 3DRT (7 single-arm studies, ^{50,51,54,55,75-77} total n=240 patients) | High | Unknown | Indirect | Imprecise | Insufficient |
| PBRT (3 single-arm studies, ^{47,52,79} total n=144 patients) | High | Unknown | Indirect | Imprecise | Insufficient |
| RFA (1 single-arm study, ⁸⁰ n=19 patients) | High | Unknown | Indirect | 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 28, the overall SOE is insufficient to form conclusions about the comparative beneficial effects or toxicities of PBRT or SBRT in the treatment of stage I NSCLC in medically operable patients. Direct outcomes of interest were overall survival, cancer-specific survival, and toxicities.

Six single-arm studies were available. The risk of bias among the studies was inherently high. The consistency of effect size direction cannot be determined in the absence of comparative studies, so this domain was deemed unknown. No direct comparative evidence is available among interventions, so this domain was deemed indirect. Because precision cannot be determined in the absence of direct comparative evidence among interventions, we deemed the evidence to be imprecise.

Table 28. Strength of evidence for local nonsurgical interventions in medically operable stage I NSCLC patients

| Treatment and Evidence Base | Risk of Bias | Consistency | Directness | Precision | Overall Strength of Evidence |
|---|--------------|-------------|------------|-----------|------------------------------|
| SBRT (5 single-arm studies, ^{48,49,81-83} total n=378) | High | Unknown | Indirect | Imprecise | Insufficient |
| PBRT (1 single-arm study, ⁴⁷ total n=28) | High | Unknown | Indirect | Imprecise | Insufficient |

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

Key Question 3

Overall, evidence from five randomized controlled trials (RCTs) and one nonrandomized comparative study is insufficient to form conclusions about the benefits (symptom relief, survival) and harms (treatment-related toxicities) of local nonsurgical 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 PDT) in symptomatic inoperable patients with obstructive endoluminal NSCLC.

Evidence from three single-arm studies of debridement and stenting is insufficient to draw conclusions about the effectiveness of those interventions.

Strength of Evidence

Brachytherapy Plus EBRT Versus Brachytherapy Alone

The evidence for comparison of brachytherapy plus EBRT versus brachytherapy alone comprised of one small RCT⁸⁵ (n=45, 15 patients per treatment arm). This trial was considered to have a high risk of bias because it failed to provide details of randomization and allocation concealment. The consistency of the evidence was unknown as it was a single RCT without confirmation from any other study. The outcomes measured in the study – symptom relief, quality of life (QOL) and treatment-related toxicities were all direct. The evidence for symptom relief, QOL and treatment-related toxicities was imprecise.

Because the evidence base that addressed these outcomes consisted of one RCT, the starting level of SOE was high (Table 29). SOE was reduced by one level each based on the high risk of bias, unknown consistency and imprecision. Therefore, compared to brachytherapy alone, the SOE that brachytherapy plus EBRT improves symptom relief, QOL and reduces treatment-related toxicities is insufficient.

Brachytherapy Plus EBRT Versus EBRT Alone

The evidence for comparison of brachytherapy plus EBRT versus EBRT alone comprised of one small RCT⁸⁶ (n=95). This trial was considered to have a high risk of bias primarily because the trial was discontinued prematurely due to lack of patient accrual and was underpowered to detect a difference in the rate of primary endpoint (rate of dyspnea). The consistency of the evidence was unknown as it was a single RCT without confirmation from any other study. The outcomes measured in the study – symptom relief, survival and treatment-related toxicities were all direct. The evidence for symptom relief, survival and treatment-related toxicities was imprecise.

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

Brachytherapy Versus EBRT

The evidence for comparison of brachytherapy versus EBRT comprised of one small RCT⁸⁷ (n=99). This trial was considered to have a very serious risk of bias because the study failed to adjust for potential confounding secondary to crossover of a large proportion of patients between treatment arms during the trial period. The consistency of the evidence was unknown as it was a single RCT without confirmation from any other study. The outcomes measured in the study – symptom relief, survival and treatment-related toxicities were all direct. The evidence for symptom relief and treatment-related toxicities was imprecise while the evidence for survival was precise.

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

treatment toxicity). Therefore, compared to EBRT, the SOE that brachytherapy improves symptom relief, survival and reduces treatment-related toxicities is insufficient.

Laser Plus Brachytherapy Versus Laser Alone

The evidence for comparison of laser plus brachytherapy versus laser alone comprised of one small RCT⁸⁸ (n=29). This trial was considered to have a high risk of bias primarily due to failure to provide details of randomization, allocation concealment and NSCLC staging of patients at the baseline. The consistency of the evidence was unknown as it was a single RCT without confirmation from any other study. The outcomes measured in the study—symptom relief, survival and treatment-related toxicities—were all direct. The evidence for symptom relief, survival and treatment-related toxicities was imprecise.

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

Laser Versus Photodynamic Therapy

The evidence for comparison of laser versus PDT comprised of one small RCT⁸⁹ (n=31). This trial was considered to have a serious risk of bias primarily because the treatment arms had imbalances at the baseline. The proportion of patients with stage III–IV cancer was much smaller in the PDT group (57%, 8 of 14) than the laser group (88%, 15 of 17) at the baseline. The consistency of the evidence was unknown as it was a single RCT without confirmation from any other study. The outcomes measured in the study—survival and treatment-related toxicities were all direct. The evidence for treatment-related toxicities was imprecise while it was precise for survival.

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

Laser Versus Electrocautery

The evidence for comparison of laser versus electrocautery comprised of one small nonrandomized comparative study⁹⁰ (n=29). This study was considered to have serious risk of bias primarily because of lack of adjustment for any potential confounders. A disproportionate number of patients had received previous treatment in the laser treated group (93 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 nonrandomized comparative study without confirmation from any other study. The outcomes measured in the study—survival and symptom relief were direct. The evidence for symptom relief and survival was imprecise.

Because the evidence base that addressed these outcomes consisted of one nonrandomized comparative study, the starting level of SOE was low (Table 30). SOE was reduced by two levels based on very serious risk of bias and by one level each for unknown consistency and

imprecision. Therefore, compared to electrocautery, the SOE that laser therapy improves survival and symptom relief is insufficient.

Table 29. Strength of comparative evidence for local nonsurgical therapies for symptoms secondary to an inoperable obstructive endoluminal NSCLC

| Treatment and Evidence Base | Outcome | Unit of Measure | Risk of Bias | Consistency | Directness | Precision | SOE |
|--|--------------------|--|--------------|-------------|------------|-----------|--------------|
| Brachytherapy plus EBRT versus brachytherapy alone (1 RCT, n=45) ⁸⁵ | 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 criteria | | | | | |
| Brachytherapy plus EBRT versus EBRT alone (1 RCT, n=95) ⁸⁶ | Symptom relief | Response rate | High | Unknown | Yes | Imprecise | Insufficient |
| | Survival | Overall survival | | | | | |
| | Treatment toxicity | Incidence | | | | | |
| Brachytherapy versus EBRT (1 RCT, n=99) ⁸⁷ | 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) ⁸⁸ | Symptom relief | Speiser's index | High | Unknown | Yes | Imprecise | Insufficient |
| | Survival | Overall survival | | | | | |
| | Treatment toxicity | Incidence | | | | | |
| Photodynamic Therapy versus Laser (1 RCT, n= 31) ⁸⁹ | Survival | Overall survival | High | Unknown | Yes | Precise | Insufficient |
| | Treatment toxicity | Incidence | High | Unknown | Yes | Imprecise | Insufficient |
| Nd-YAG versus Electrocautery (1 NRC, n=29) ⁹⁰ | Survival | Mean survival | High | Unknown | Yes | Imprecise | Insufficient |
| | Symptom relief | % response | | | | | |

BT = 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

Table 30. Strength of noncomparative evidence for local nonsurgical therapies for symptoms secondary to an inoperable obstructive endoluminal NSCLC

| Treatment and Evidence Base | Risk of Bias | Consistency | Directness | Precision | Overall Strength of Evidence |
|---|--------------|-------------|------------|-----------|------------------------------|
| RFA (1 study, n=33) ⁹¹ | High | Unknown | Indirect | Imprecise | Insufficient |
| BT + STNT (1 study, n=10) ⁹² | High | Unknown | Indirect | Imprecise | Insufficient |
| LASR + STNT (1 study, n=52) ⁹³ | High | Unknown | Indirect | Imprecise | Insufficient |

BT = brachytherapy; LASR = laser; n = total sample size of the study; NSCLC = non-small-cell lung cancer; RFA = radiofrequency ablation; STNT = stenting

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 nonsurgical 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.¹⁷ The authors of that review reported limited, noncomparative published data are available to assess outcomes in this setting. An Agency for Healthcare Research and Quality (AHRQ) Technical Brief reported on the state of the evidence for SBRT in a number of cancers, including NSCLC.¹⁰⁴ The authors of this Technical Brief did not identify any published RCTs 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 RCTs that compared local nonsurgical bronchoscopic interventions in patients with an endobronchial NSCLC. We found five RCTs of poor quality and one nonrandomized comparative study that compared six unique combinations of bronchoscopic interventions in NSCLC patients. Evidence is insufficient 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 PDT

Evidence from three single-arm studies of debriement and stenting is insufficient to draw conclusions about the effectiveness of those interventions.

We found one Cochrane systematic review³⁴ 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 nonsurgical 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 Guidelines¹⁰⁵ for palliative care of lung cancer patients relevant in part to the current context of local nonsurgical 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, PDT, electrocautery and stenting. The ACCP guidelines¹⁰⁵ 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 nonsurgical therapies for stage I NSCLC. The evidence for Key Questions 1 and 2 does not reach that level, so we have primarily limited comments to relevance of the PICOTS (Population, Intervention, Comparator, Outcomes, Timing, Setting) elements.⁴⁶ The PICOTS format comprises a practical and useful structure to review applicability in a systematic manner. These factors are summarized in Table 31 for Key Questions 1 and 2.

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

Table 31. Summary of applicability of evidence for Key Questions 1 and 2

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

Multiple shortcomings with the current evidence base preclude interpretation about general applicability. Firstly, the comparative benefits and harms of various endobronchial treatments are still unknown because of lack of good quality RCTs. 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 underrepresented in the current data. Factors that affect the applicability of the findings of this CER to practice are summarized in Table 32.

Table 32. Summary of applicability of evidence for Key Question 3

| Domain | Applicability of Evidence |
|---------------|---|
| Populations | <ul style="list-style-type: none"> The patients in the studies included in this report appear 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 | <ul style="list-style-type: none"> The single modality interventions (brachytherapy, EBRT, electrocautery, laser, photodynamic, debridement, stenting) 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 | <ul style="list-style-type: none"> See above for Intervention |
| Outcomes | <ul style="list-style-type: none"> The major outcomes of interest were symptom relief, overall survival, disease specific survival, quality of life and treatment-related toxicity. Although OS is the primary 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),¹⁰⁶ 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. |
| Timing | <ul style="list-style-type: none"> The relevant periods occur at the time of treatment through followup over months (palliation) or years (overall survival). |
| Setting | <ul style="list-style-type: none"> The outcomes of local bronchoscopic therapies largely depend on the expertise of the provider and the center providing these services. We could not assess the impact of such operating characteristics on the treatment outcomes because these data were not available in the published papers. |

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

Implications for Clinical and Policy Decisionmaking

Our results show no direct comparative evidence to support a decision among 3DRT, PBRT, RFA, or SBRT in stage I NSCLC patients. Comparative evidence is sparse among any of the interventions considered in Key Question 3.

In the absence of 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 Key Questions 1 and 2. It may reach 3 weeks or more for 3DRT or intensity-modulated radiation therapy (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 (www.proton-therapy.org), PBRT is available for NSCLC therapy at 10 specialized centers in the United States, 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.^{107,108} The survey results indicated nearly 64 percent (95% confidence interval [CI], 60–68%) 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, decisionmakers 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 Key Questions were a driver of development of this CER. Its findings ideally would provide a foundation for critically considering each technology in terms of the evidence available. However, it is unclear whether this CER will ultimately affect policy decisions.

Limitations of the Comparative Effectiveness Review Process

At the time of initiation of this CER, we expected that the total evidence base would be substantial. The volume of literature identified in the AHRQ Topic Development and Refinement process suggested the existence of a robust evidence base for all Key Questions. However, when we began to screen articles, it became evident that very few published comparative studies exist overall, none for Key Questions 1 and 2 and only six for Key Question 3.

Limitations of Evidence Base

Key Questions 1 and 2

The primary limitation is lack of comparative trials of any design for Key Questions 1 and 2. Percutaneous image-guided RFA has been investigated as an option for the treatment of stage I NSCLC. In our review, we found that RFA studies in lung primarily comprise heterogeneous case series that are complicated by several factors. First, many reports included metastatic and primary lesions from non-lung and lung sites, but did not stratify outcomes such as overall

survival according to tumor stage or type. Second, the technical details of RFA, such as the type of equipment used, the power settings or wattage delivered, and details of followup assessment and subsequent therapy, were not consistent or consistently reported across studies. These factors conspired to severely limit RFA study selection in the report.

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

Key Question 3

The body of evidence available for Key Question 3 comprised five RCTs, one nonrandomized comparative study and three relevant single arms from three otherwise comparative studies. We included the latter three study arms because we did not have higher level evidence for the interventions in question, debriement and stenting. Significant limitations in the quality and quantity of the evidence base led us to conclude that the evidence was insufficient to make conclusions about comparative effectiveness of local nonsurgical interventions to treat endobronchial obstructions in NSCLC patients. There was only one comparative 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 U.S. Preventive Services Task Force (USPSTF) study quality; often the studies were small and not powered to detect a prespecified clinically meaningful difference in a standardized outcome of interest thereby limiting their utility beyond hypothesis generation. Most studies lacked details about randomization and allocation concealment. The one nonrandomized comparative study available for Key Question 3 did not use statistical adjustment to reduce confounding; such adjustment for confounding should be consistently used in nonrandomized studies.

Research Gaps

Overview

Key Question 1 considers the relative clinical effectiveness of local nonsurgical interventions—3DRT, SBRT, PBRT and RFA—as sole therapy for patients with stage I NSCLC who are deemed to be medically inoperable. Key Question 2 addresses the same set of interventions in patients with stage I NSCLC who are deemed operable but who decline resection. The evidence base for Key Questions 1 and 2 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 SOE is insufficient to draw conclusions on the comparative effectiveness of the interventions in terms of overall survival or cancer-specific survival.

Key Question 3 compared outcomes of available local endobronchial interventions used with curative or palliative intent to treat airway obstruction. There was only one comparative study available per six unique treatment comparisons to draw inferences about comparative effectiveness. Evidence on the patient outcomes was limited and, as such, is insufficient to make conclusions on the comparative effectiveness of the interventions in terms of symptom relief, overall survival or cancer-specific survival and harms of the treatment.

Key Questions 1 and 2

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

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

We found no direct comparative evidence in this CER on the relative clinical effectiveness among any of the local nonsurgical interventions we evaluated: RFA, SBRT, 3DRT, IMRT or PBRT. As part of this review, we searched for ongoing clinical trials of these technologies in stage I NSCLC. In the process, we identified two international randomized, phase 3 clinical trials of surgical resection versus SBRT that are recruiting patients (NCT01336894 and NCT00840749). However, neither of these trials will reveal relative outcomes among local nonsurgical interventions in stage I NSCLC. Thus, we suggest prospective studies are needed to properly evaluate the relative clinical benefits and harms of the technologies evaluated in this CER, taking into account the potential impediments to study we discuss below. Ideally, comparative studies in medically inoperable or operable stage I NSCLC patients would incorporate the following:

- To assure comparability of patients and minimize bias, standardized patient selection criteria would be used that involve consultation including a thoracic surgeon, medical oncologist, and radiation oncology specialist. Key factors to consider include comorbidity status (particularly cardiopulmonary function and capacity), age, performance status, tumor size and tumor location.
- Standardized intervention protocols with training and quality assurance programs within and across participating institutions are necessary for the best study. For radiotherapy, key factors would include the imaging and planning method, immobilization method, dose and fractionation schedule, and the biologically effective dose (BED) for comparisons of different modalities (e.g., SBRT, 3DRT, IMRT, PBRT). For RFA, issues would include treatment power and duration in the context of tumor size and location.
- Prespecified followup criteria and methods, in particular notation of subsequent systemic therapy administered at recurrence, are key considerations. Subsequent systemic therapy

is a key concern because it is impossible to discern the effect of an intervention followed by systemic therapy at progression from that achieved with the intervention alone. Is the effectiveness a function of the systemic therapy, the intervention, or the combination?

- Rigorous and standardized reporting is needed to account for all patients and treatments received. Data for operable and inoperable patients would be reported separately. Rigorous methods for conduct of RCTs is urged, particularly intent-to-treat analysis and adjustment of survival data to account for patients who develop recurrent disease and subsequently receive systemic chemotherapy as part of their treatment plan.
- Primary outcomes would include overall survival, cancer-specific survival, and local control. Prespecified, systematic collection of adverse events (AEs) using validated criteria (e.g., CTCAE criteria) is necessary to permit accurate assessment of relative benefits and risks of the interventions.

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

The general dissemination of conformal radiotherapy technologies into community clinical practice, most lately and specifically SBRT^{107,108} is a potential impediment to comparative study of those technologies. Published survey results show that nearly 40 percent of solo practitioners treat patients with SBRT, which suggests that this technology is now accessible and its efficacy accepted in the broader radiation oncology community.^{107,108} In addition, the shorter hypofractionated SBRT course is more “patient friendly” than those associated with conventionally fractionated conformal radiotherapy methods. This patient-specific advantage may represent an additional reason why SBRT has rapidly disseminated into clinical practice in the absence of direct comparative clinical trial evidence to support its reputation of clinical superiority over conventionally fractionated conformal techniques. We also recognize a number of other significant – perhaps insurmountable – technical impediments to conducting adequate comparative studies among the most widely available conformal radiotherapy-based modalities and other interventions such as RFA. These are outlined below.

Practical limitations exist to complicate comparative study of RFA and the conformal radiotherapy modalities in the stage I NSCLC setting. Although we did not evaluate these issues in this CER, it is generally thought that a tumor size greater than 4 cm, or a tumor location less than 1 cm from the hilum or large vessels, preclude the use of RFA.^{28,109} Current clinical wisdom suggests RFA is best suited for patients with peripherally located, smaller lesions, due to the “heat sink” effect of large blood vessels that dissipates heat from the tumor and reduces its efficacy.¹⁰⁹⁻¹¹¹ By contrast, although we didn’t investigate any relationship in our systematic review, conformal radiotherapy-based modalities, particularly SBRT, have been used in patients with either peripheral or central tumors, as well as tumors > 4 and up to 7 cm in diameter, the latter corresponding to stage IB (T2N0M0).⁴ Furthermore, radiotherapy effectiveness is not subject to a “heat sink” effect, as is RFA. Given those caveats, recruitment and accrual of sufficient numbers of similar stage I NSCLC patients to make clinically meaningful, relevant comparisons between RFA or conformal radiotherapy-based treatments would be difficult.

A key technical issue in comparing the radiotherapy interventions likely is the significant difference in the BED of radiation that can be safely delivered by SBRT, compared to IMRT or 3DRT delivered with conventional fractionation protocols. In brief, radiation therapy for NSCLC typically is delivered to a total dose of 60-70 Gray (Gy); SBRT delivers that dose in three to five fractions of 20 Gy each (estimated BED = 180 Gy₁₀ using standard principles) whereas

conventionally fractionated IMRT or 3DRT delivers 60-70 Gy in 30 fractions of 2 Gy each in 4 to 5 weeks, yielding an estimated BED of 72 Gy₁₀. The difference in the attainable BED is considered to have potential efficacy implications.¹¹² The higher BED causes tumor ablation, rather than tumor cell kill, allowing for little to no tumor cell repopulation between doses of radiation.

In this CER, we did not systematically investigate whether a higher BED delivered by any conformal radiotherapy modality can be associated with better clinical outcomes - such as overall survival - compared to a lower BED. This has been reported in published single-arm studies reviewed in this CER, for example the large, multicenter, retrospective series on SBRT in Japan by Onishi and colleagues.⁸⁴ However, we are not aware of any direct comparative evidence on this topic among any of the conformal radiotherapy technologies, so it is not possible to make even indirect comparisons between the delivered BED and clinical outcomes in any case. Furthermore, we are aware of no published clinical trial evidence to ascertain whether a higher BED delivered by SBRT is associated with differences in patient outcomes compared to a lower BED delivered either by SBRT or by a conventionally fractionated conformal radiotherapy modality. We acknowledge the difference in delivered BED has biologically plausible clinical implications, and perhaps ethical implications, that would need to be addressed in designing a study of any type to compare conformal radiotherapy-based technologies. But, it is not clear to us that the BED issue under discussion here is settled.

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

Key Question 3

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

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

- Lack of comparative evidence generated from adequately powered RCTs regarding the benefits and harms of various bronchoscopic interventions used for treating endoluminal obstructions in patients with NSCLC.
- Lack of comparative evidence generated from good quality RCTs regarding the QOL data from patients who receive various bronchoscopic interventions used for treating endoluminal obstructions in patients with NSCLC.
- Need for systematic collection of treatment-related toxicities data from various bronchoscopic interventions used for treating endoluminal obstructions from actual clinical practice setting.

During our review, we identified two RCTs that aimed to compare local endobronchial interventions in patients with endobronchial NSCLC. However, both these trials were not completed due to lack of patient accrual. Among these two RCTs, the trial by Moghissi et al.,¹⁰² is most notable. The objective of this trial was to compare two treatment policies in terms of symptom relief, respiratory function, performance status, QOL and survival. This study planned to recruit 400 patients in 3 years at 24 clinical centers in the 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 Langendijk⁸⁶ that randomized patients to brachytherapy plus EBRT or EBRT alone arm was discontinued due to lack of patient accrual before completing the planned enrollment of 160 patients.

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

NSCLC patients with endoluminal obstructions are particularly difficult to randomize in trials because of many reasons particularly ethical issues. Most of these bronchoscopic interventions are considered complementary and are used sequentially in a clinical setting¹¹³ and therefore randomizing critically ill patients to either therapy alone has ethical implications. Further, many of these patients present with an impending obstruction and immediate symptom relief is foremost. Obtaining informed consent in such a situation is a barrier in patient recruitment. These reasons are likely to obviate successful conduct of a future RCT.

Thus, 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 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 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 would be measured in such a study would include symptom control, QOL, survival and treatment-related AEs. Data related to symptom control would be captured using a standardized validated tool applied uniformly across all interventions. 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 assess symptom control to allow objective and uniform measurements of symptom control. Generic instruments such as Short Form 36 Health Survey (SF-36) and EuroQOL 5 dimension (EQ-5D) would be used in conjunction with lung cancer specific measures such as European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) modules C30 and LC13 and Functional Assessment of Cancer Therapy- Lung (FACT-L) to measure QOL data.

Treatment-related AEs would be assessed from the date of the procedure extending to a reasonable time preferably until death using standardized and well-defined criteria with an independent causality analysis. A process to capture AEs that occur when patients are not under direct medical supervision (such as home or long term care facility) would also be prespecified

in the study protocol. Data on all potential prognostic covariates would include but not be limited to patient characteristics (age, sex, race, performance status, comorbidities), disease characteristics (tumor stage, histopathology, location, size, blockage) and technical attributes of the procedure (technical success, technical variables related to use of procedures, type of instrument used) as well 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 registries¹¹⁴ for evaluating patient outcomes, registries need to be created with a question in mind which guides 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 AEs.

Conclusion

We conducted a systematic review of the literature to evaluate the comparative effectiveness of local nonsurgical 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 Key Questions 1 and 2 we included only single local nonsurgical interventions: 3DRT, PBRT, RFA, and SBRT. For Key Question 3 we allowed combinations of local nonsurgical therapies including neodymium-doped yttrium aluminum garnet (Nd-YAG) laser, PDT, endobronchial debridement with stenting, and EBRT, as well as systemic chemotherapy.

Evidence for both Key Questions 1 and 2 consists only of single-arm studies, with no direct comparisons among interventions. The best evidence for Key Question 3 consists of RCTs of one comparison only, precluding indirect comparisons. Evidence from single-arm studies also is available for several interventions relevant to Key Question 3. 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, QOL, symptomatic relief and toxicities.

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Abbreviations

| | |
|-----------|---|
| 3DRT | Three-dimensional radiation therapy |
| ACE-27 | Adult Co-Morbidity Evaluation-27 scoring system |
| BED | Biologically Effective Dose |
| CGE | Cobalt Gray equivalent |
| CI | Confidence interval |
| CSS | Cancer-specific survival |
| CT | Computed Tomography |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| 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 |
| FACT-L | Functional Assessment of Cancer Therapy- Lung |
| FDG | Fluorodeoxyglucose |
| FEV | Forced expiratory volume |
| FRS | Fractions |
| GY | Gray |
| IMRT | Intensity-modulated radiotherapy |
| KPS | Karnofsky performance status |
| LCS | Lung Cancer Subscale |
| LCT | Local control |
| LENT-SOMA | Late Effects Normal Tissue Task Force -Subjective, Objective, Management, Analytic scales |
| MeV | Million electron volts |
| mos | Months |
| N | Number |
| NA | Not applicable |
| NOS | Not otherwise specified Non-small-cell Lung Cancer |
| NR | Not reported |
| NSCLC | Non-small-cell lung cancer |
| OS | Overall Survival |
| PCS | Physical Component Summary |
| PDT | Photodynamic therapy |
| PS | Performance status |
| Pts | Patients |
| QLQ | Quality of life Questionnaire |
| QOL | Quality of life |
| RFA | Radiofrequency ablation |
| RT | Radiation Therapy |
| RTOG | Radiation Therapy Oncology Group |
| Rx | Treatment |

| | |
|------|---------------------------------------|
| SAS | Single arm study |
| SBRT | Stereotactic body radiotherapy |
| UICC | Union Internationale Contre le Cancer |
| WHO | World Health Organization |
| YAGL | Yttrium aluminum garnet laser |

Appendix A. Search Strategy

The following electronic databases were searched by a medical librarian for citations:

- MEDLINE® (January 1995 to December 12, 2011) yielded 2883 records
- EMBASE® (January 1995 to December 13, 2011) yielded 1318 records
- Cochrane Controlled Trials Register (through December 13, 2011) yielded 99 records
- Search update of all three databases during peer review: (December 14, 2011-July 25, 2012) yielded 348 records

MEDLINE

Stage I

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

AND

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

AND

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

AND

English language/Humans as limits

Advanced

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

AND

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

AND

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

AND (endoscopy OR endoscopic OR endobronchial))

AND

English language/Humans as limits

EMBASE

Stage I

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

AND

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

AND

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

AND

English language/Humans as limits

AND NOT MEDLINE

Advanced

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

AND

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

AND

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

AND

English language/Humans as limits

AND NOT MEDLINE

COCHRANE

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

Search Strategy For Gray Literature

Regulatory Information

FDA (Drugs@FDA)

Source: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm>

Date searched: 5/30/12

Search strategy: "RF 3000," RF 3000 Radiofrequency Ablation System (Boston Scientific); "RITA StarBurst," RITA StarBurst Radiofrequency Ablation System (Angiodynamics (formerly RITA)); "Elektrotom 106," Berchtold Elektrotom 106 HFTT (Berchtold Corp.); "OncoSeed," OncoSeed(Oncura), "Best Iodine 125," Best Iodine-125 (Best Medical International, Inc); "Best Palladium 103 Seeds" Best Palladium-103 Seeds(Best Medical International, Inc.); "VariSource HDR afterloader," VariSource HDR afterloader (Varian Medical Systems); "GammaMedplus afterloader," GammaMedplus (Varian Medical Systems); "Clinac Linear Accelerator," Clinac Linear Accelerator(Varian Medical Systems); "Varian Trilogy system," Trilogy system (Varian Medical Systems); "Varian TrueBeam," TrueBeam (Varian Medical Systems); "Novalis," Novalis Tx (Varian Medical Systems); "ONCOR," ONCOR Impression & ONCOR Expression (Siemens Medical Solutions USA, Inc); "Primatom," Primatom (Siemens Medical Solutions USA, Inc); "Optivus PBTS," Proton Beam Therapy System (PBTS) (Optivus); "PT2 Varian Proton Therapy System," PT2 Varian Proton Therapy System (Varian Medical Systems); "Proteus One," Proteus One (IBA Particle Therapy); "Hood stent," Hood stent with rings (Hood Laboratories); "Plyflex stent, Ultraflex Metallic stents," Plyflex stent & Ultraflex Metallic stents (Boston Scientific); "Bryan Dumon," Bryan-Dumon Series II (Bryan Corporation); "Nd-YAG Laser," Nd-YAG Laser (Lee Laser Inc., Crystal Laser, & PowerTechnology Inc.)

Records: 0

Clinical Trial Registries

ClinicalTrials.gov

Source: <http://clinicaltrials.gov/>

Date searched: 5/30/12

Search strategy: ("NSCLC" OR "non-small cell") AND (("stage I") OR ("stage III" OR "stage IV")) | Closed Studies | Exclude Unknown | Phase 3, 4

Records: 81

Unpublished records: 1: NCT00687986

Conference Papers and Abstracts

- American Society of Clinical Oncology
- American Society for Radiation Oncology

Date searched: 5/30/12

Search strategy: ("NSCLC" OR "non-small cell") AND ("stage I" OR "stage III" OR "stage IV")

Records: 493

Manufacturer Database

Source: Covidien

Date posted: 5/24/12

Search strategy: Not applicable

Records: 95

Source: Accuray

Date posted: 5/24/12

Search strategy: Not applicable

Records: 74

Source: Elekta

Date posted: 5/24/12

Search strategy: Not applicable

Records: 11

Source: Loma Linda

Date posted: 5/24/12

Search strategy: Not applicable

Records: 5

Appendix B. Excluded Studies

Appendix Table B1. Key to study exclusion coding system

| Code | Definition |
|------|--------------------------------|
| FLA | Foreign language article |
| NRD | Not relevant design |
| NRP | Not relevant population |
| NRI | Not relevant intervention |
| NRO | Not relevant outcome |
| OPP | Overlapping patient population |
| USD | Unclear study description |
| UTO | Unable to obtain full text |

Abacioglu, P. F. Yumuk, H. Caglar, M. Sengoz and N. S. Turhal. Concurrent chemoradiotherapy with low dose weekly gemcitabine in stage III non-small cell lung cancer. *BMC Cancer* 2005 5(): 71. NRP

Abe, J. Takahashi, H. Fukuda, S. Ono, S. Yoshioka, T. Akaizawa, K. Kubota, K. Yamada, T. Takahashi, K. Ohkuda, N. Asoh, M. Yonechi, N. Maehira, Y. Mariya and M. Aoki. A phase II study of cisplatin, oral administration of etoposide, OK-432 and radiation therapy for inoperable stage III non-small cell lung cancer. *International Journal of Clinical Oncology* 1998 3(6): 365-369. NRP

Abratt, L. J. Shepherd and D. G. Salton. Palliative radiation for stage 3 non-small cell lung cancer--a prospective study of two moderately high dose regimens. *Lung Cancer* 1995 13(2): 137-43. NRP

Adelstein, T. W. Rice, L. A. Rybicki, J. F. Greskovich, Jr., J. P. Ciezki, M. A. Carroll and M. M. DeCamp. Accelerated hyperfractionated radiation, concurrent paclitaxel/cisplatin chemotherapy and surgery for stage III non-small cell lung cancer. *Lung Cancer* 2002 36(2): 167-74. NRP

Adkison, D. Khuntia, S. M. Bentzen, G. M. Cannon, W. A. Tome, H. Jaradat, W. Walker, A. M. Traynor, T. Weigel and M. P. Mehta. Dose escalated, hypofractionated radiotherapy using helical tomotherapy for inoperable non-small cell lung cancer: preliminary results of a risk-stratified phase I dose escalation study. *Technol Cancer Res Treat* 2008 7(6): 441-7. NRI

Aerts, A. A. van Baardwijk, S. F. Petit, C. Offermann, J. Loon, R. Houben, A. M. Dingemans, R. Wanders, L. Boersma, J. Borger, G. Bootsma, W. Geraedts, C. Pitz, J. Simons, B. G. Wouters, M. Oellers, P. Lambin, G. Bosmans, A. L. Dekker and D. De Ruyscher. Identification of residual metabolic-active areas within individual NSCLC tumours using a pre-radiotherapy (18)Fluorodeoxyglucose-PET-CT scan. *Radiother Oncol* 2009 91(3): 386-92. NRO

Aerts, V. Surmont, R. J. van Klaveren, K. Y. Tan, S. Senan, G. van Wijhe, R. Vernhout, G. T. Verhoeven, H. C. Hoogsteden and J. P. van Meerbeeck. A phase II study of induction therapy with carboplatin and gemcitabine among patients with locally advanced non-small cell lung cancer. *J Thorac Oncol* 2006 1(6): 532-6. NRP

Ahmad, A. P. Sandhu, M. M. Fuster, K. Messer, M. Pu, P. Nobiensky, L. Bazhenova and S. Seagren. Hypofractionated radiotherapy as definitive treatment of stage I non-small cell lung cancer in older patients. *Am J Clin Oncol* 2011 34(3): 254-8. NRI

Ahmed, J. Bedford, J. Warrington and M. Hawkins. Volumetric modulated arc radiotherapy (VMAT) of tumours in the thorax-acute toxicity results from a single centre. *Radiotherapy and Oncology* 2011 99(): S499. NRD

Ahn, K. Park, D. Y. Kim, K. M. Kim, J. Kim, Y. M. Shim, K. S. Lee, J. Han, H. J. Kim, J. Kwon, D. H. Lim, Y. J. Noh, J. E. Lee and S. J. Huh. Preoperative concurrent chemoradiotherapy for stage IIIA non-small cell lung cancer. *Acta Oncol* 2001 40(5): 588-92. NRP

Ahn, M. S. Han, J. H. Yoon, S. Y. Jeon, C. H. Kim, H. J. Yoo and J. C. Lee. Treatment of stage I non-small cell lung cancer with CyberKnife, image-guided robotic stereotactic radiosurgery. *Oncol Rep* 2009 21(3): 693-6. NRO

Ahn, Y. C. Kim, K. S. Kim, K. O. Park, W. K. Chung, T. K. Nam, B. S. Nah, J. Y. Song and M. S. Yoon. Results of curative radiation therapy with or without chemotherapy for stage III unresectable non-small cell lung cancer. *Cancer Res Treat* 2005 37(5): 268-72. NRP

Aich, K. Bhattacharaya, P. Gupta and P. K. Sur. Hypofractionated radiotherapy (MRC trial) - A preferred schedule for locally advanced non-small cell lung cancers. *Indian Journal of Radiology and Imaging* 1998 8(3): 177-181. UTO

Aisner, C. P. Belani, C. Kearns, B. Conley, D. Hiponia, C. Engstrom, E. Zuhowski and M. J. Egorin. Feasibility and pharmacokinetics of paclitaxel, carboplatin, and concurrent radiotherapy for regionally advanced squamous cell carcinoma of the head and neck and for regionally advanced non-small cell lung cancer. *Semin Oncol* 1995 22(5 Suppl 12): 17-21. NRP

Ajlouni, R. Chapman and J. H. Kim. Accelerated-interrupted radiation therapy given concurrently with chemotherapy for locally advanced non-small cell lung cancer. *Cancer J Sci Am* 1996 2(6): 314-20. NRP

Akerley and H. Choy. Concurrent paclitaxel and thoracic radiation for advanced non-small cell lung cancer. *Lung Cancer* 1995 12 Suppl 2(): S107-15. NRP

Akerley and H. Choy. Single-agent paclitaxel and radiation for non-small cell lung cancer. *Semin Radiat Oncol* 1999 9(2 Suppl 1): 85-9. NRP

Akerley, J. E. Herndon, Jr., A. P. Lyss, H. Choy, A. Turrisi, S. Graziano, T. Williams, C. Zhang, E. E. Vokes and M. R. Green. Induction paclitaxel/carboplatin followed by concurrent chemoradiation therapy for unresectable stage III non-small-cell lung cancer: a limited-access study--CALGB 9534. *Clin Lung Cancer* 2005 7(1): 47-53. NRP

Albain, J. J. Crowley, A. T. Turrisi, 3rd, D. R. Gandara, W. B. Farrar, J. I. Clark, K. R. Beasley and R. B. Livingston. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol* 2002 20(16): 3454-60. NRP

Albain, R. S. Swann, V. W. Rusch, A. T. Turrisi, 3rd, F. A. Shepherd, C. Smith, Y. Chen, R. B. Livingston, R. H. Feins, D. R. Gandara, W. A. Fry, G. Darling, D. H. Johnson, M. R. Green, R. C. Miller, J. Ley, W. T. Sause and J. D. Cox. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009 374(9687): 379-86. NRP

Albain, V. W. Rusch, J. J. Crowley, T. W. Rice, A. T. Turrisi, 3rd, J. K. Weick, V. A. Lonchyna, C. A. Presant, R. J. McKenna, D. R. Gandara and et al.. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol* 1995 13(8): 1880-92. NRP

Alberto, R. O. Mirimanoff, B. Mermillod, S. Leyvraz, H. Nagy-Mignotte, M. Bolla, D. Wellmann, D. Moro and E. Brambilla. Rapidly alternating combination of cisplatin-based chemotherapy and hyperfractionated accelerated radiotherapy in split course for stage IIIA and stage IIIB non-small cell lung cancer: results of a phase I-II study by the GOTHA group. *Group d'Oncologie Thoracique des Regions Alpes*. *Eur J Cancer* 1995 31A(3): 342-8. NRP

Alexander, M. Othus, H. B. Caglar and A. M. Allen. Tumor volume is a prognostic factor in non-small-cell lung cancer treated with chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2011 79(5): 1381-7. NRP

Ali, M. J. Kraut, M. Valdivieso, A. J. Wozniak, G. Cummings and G. P. Kalemkerian. A phase II study of mitomycin C, etoposide, and cisplatin in advanced non-small cell lung cancer. *Cancer Invest* 2000 18(1): 1-5. NRP

Allison, A. Schulsinger, K. H. Shin and V. Vongtama. Chemoradiation enhances response in stage IIIB lung cancer. *Radiation Oncology Investigations* 1996 4(4): 171-175. NRP

Ambrogi, O. Fanucchi, R. Cioni, P. Dini, A. De Liperi, C. Cappelli, F. Davini, C. Bartolozzi and A. Mussi. Long-Term Results of Radiofrequency Ablation Treatment of Stage I Non-small Cell Lung Cancer: A Prospective Intention-to-Treat Study. *J Thorac Oncol* 2011 6(12): 2044-51. NRP

Ambrogi, P. Dini, F. Melfi and A. Mussi. Radiofrequency ablation of inoperable non-small cell lung cancer. *J Thorac Oncol* 2007 2(5 Suppl): S2-3. NRP

Ampil and S. V. Sanghani. Timing of radiotherapy in asymptomatic patients with inoperable non-small cell lung cancer: a survival analysis and literature review. *Radiat Med* 1996 14(4): 211-4. NRP

Anacak, N. Mogulkoc, S. Ozkok, T. Goksel, A. Haydaroglu and U. Bayindir. High dose rate endobronchial brachytherapy in combination with external beam radiotherapy for stage III non-small cell lung cancer. *Lung Cancer* 2001 34(2): 253-9. NRP

Anderson, J. J. McAleer, S. Stranex and G. Prescott. Radical radiotherapy for inoperable non-small cell lung cancer: what factors predict prognosis?. *Clin Oncol (R Coll Radiol)* 2000 12(1): 48-52. NRI

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Appendix C. Evidence Tables

Appendix Table C1. Description of studies that address Key Question 1

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|-------------------------------------|--|---|--|--|---|
| Andratschke-2011, Germany, #132 | Study design: RET, SAS Patients enrolled: 92 (100%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Histologically proven NSCLC stage 1 not suitable for surgery for medical or functional reasons Exclusion criteria: 1. Patients with mediastinal lymph node metastases | Stage I: 92 (100%) | Location: Central: 24 (26%) Peripheral: 68 (74%) Histopathology: AC: 35 (38%) SCC: 49 (53%) BAC: 2 (2%) NOS: 6 (7%) | Age (years): 75 (53-93) Women: 28 (30%) Race: NR Comorbidities: COPD: 76 (83%) CVD: 37 (40%) Performance status: KPS: 70 (60–100) ≤70: 16 (17%) 70: 50 (54%) >70: 26 (28%) |
| Baumann-2006, Sweden, Denmark, #271 | Study design: RET, SAS Patients enrolled: Total: 141 (100%) Medically inoperable: 136 (96%) Refused surgery: 5 (4%) Lost to FU/excluded/missing: Lost to follow up: 3 (2%) (Baseline data based on 141 Patients, outcome data based on 138 Patients) | Inclusion criteria: NR Exclusion criteria: NR | Stage I: 141 (100%) | Location: NR Histopathology: AC: 44(31%) SCC: 39(28%) BAC: 3 (2%) NOS: 21 (15%) Unknown: 31 (24%) | Age (years): 74 (56-90) Women: 72 (51%) Race: NR Comorbidities: COPD: 78(55%) CVD: 25 (18%) COPD + CVD: 21(15%) Other malignancies: 14(10%) Other compromising disease: 3 (2%) Performance status: NR |
| Baumann-2009, Sweden, Norway, | Study design: RET, SAS | Inclusion criteria: 1. Stage 1 Peripherally located NSCLC. | Stage I (T1): 37 (65%) Stage I (T2): 20 (35%) | Location: Superior: 37 (65%) Inferior: 16 (28%) | Age (years): 75 (59-87) |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|------------------------------|---|--|---------------------|--|--|
| Denmark, #270 | <p>Patients enrolled: SBRT Total: 60 (100%) Medically inoperable: 56 (99%) Refused surgery: 1 (2%)</p> <p>Lost to FU/excluded/missing: Lost to follow-up: 1 (2%) Excluded due to being given inadequate doses: 2 (4%)</p> | <p>2. Consent</p> <p>Exclusion criteria: 1. Central tumor growth adjacent to trachea, main bronchus, or esophagus 2. Prior malignancy within the past 5 years</p> | | <p>Middle: 4 (7%)</p> <p>Histopathology: AC: 19 (33%) SCC: 8(14%) LCC: 1 (2%) NOS: 10 (18%) Unknown: 19 (33%)</p> | <p>Women: 31 (54%)</p> <p>Race: NR</p> <p>Comorbidities: COPD: 40 (70%) CVD: 14 (26%) COPD & CVD: 8 (14%) Lung Fibrosis: 1 (2%) Advanced Age (years) + joint disease: 1 (2%)</p> <p>Mean FEV1%: 64 (20-162)</p> <p>Performance status: KPS: 80 (70-90) 70: 4 (7%) 80: 36 (63%) 90: 17 (30%)</p> |
| Bogart-2010, USA, #382 | <p>Study design: PRO, SAS</p> <p>Patients enrolled: 39 (100%)</p> <p>Lost to FU/excluded/missing: Declined treatment: 1</p> | <p>Inclusion criteria: 1. A histologic or cytologic diagnosis of stage IA or IB NSCLC with a solitary parenchymal lung lesion measuring ≤ 4 cm 2. Patients at high risk for complications after standard lobectomy, as defined by pulmonary dysfunction 3. Have high-risk features of comorbid medical illness making them unsuitable for surgical resection 4. ECOG performance status of 0 to 2 5. Weight loss less than 10% in the 6 months before protocol entry</p> <p>Exclusion criteria: 1. Prior chemotherapy for lung cancer 2. Prior radiotherapy to the chest</p> | Stage I: 39 (100%) | <p>Location: NR</p> <p>Histopathology: NOS: 39 (100%)</p> | <p>Age (years): 75 (48-87)</p> <p>Women: 21 (53%)</p> <p>Race: NR</p> <p>Comorbidities: (N=38) Median FEV1:0.96 95% CI: (0.83 to 1.31)</p> <p>Eleven (28%) of 39 patients required supplemental oxygen, between 2 and 4 L nasal canula, before the start of therapy.</p> <p>Performance status: ECOG: 0: 2 (5%) 1: 26 (67%) 2: 11 (28%)</p> |
| Bollineni-2012, Netherlands, | <p>Study design: RET, SAS</p> | <p>Inclusion criteria: Patients not suitable for surgery</p> | Stage I: 132 (100%) | <p>Location: Not stated</p> | <p>Age (years): 75 (46-90)</p> |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|-------------------------|---|---|---------------------------|---|--|
| #4548 | <p>Patients enrolled: 132 (100%)</p> <p>Lost to FU/excluded/missing: 0</p> | <p>for medical or functional reasons with a solitary FDG-PET positive lesion in the lung</p> <p>Exclusion criteria: Not stated</p> | | <p>Histopathology: NSCLC not stated Pathological confirmation: 40 (30%)</p> | <p>Women: 37 (28%)</p> <p>Race: NR</p> <p>Comorbidities: Median CCI: 4 (2-12)</p> <p>Performance status: WHO 0-1: 106 (80%) 2-3: 26 (20%)</p> |
| Bradley-2003, USA, #445 | <p>Study design: PRO, SAS</p> <p>Patients enrolled: 56 (100%)</p> <p>Lost to FU/excluded/missing: NR</p> | <p>Inclusion criteria: 1. Histologically proven NSCLC</p> <p>Exclusion criteria: 1. Patients treated with only palliative intent (\leq 60 Gy)</p> | Stage I: 56 (100%) | <p>Location: Upper lobe: 35 (62%) Middle or lower lobe: 21 (38%)</p> <p>Histopathology: AC: 14 (25%) SCC: 25 (44%) LCC: 6 (11%) NOS: 11 (20%)</p> | <p>Age (years): 73 (52-90)</p> <p>Women: 32 (57%)</p> <p>Race: White: 43 (77%) Black: 13 (23%)</p> <p>Comorbidities: KFI Comorbidity Score: 0: 10 (18%) 1: 19 (32%) 2: 14 (25%) 3: 13 (23%)</p> <p>Performance status: KPS: \geq 70: 49 (88%) < 70: 7 (12%)</p> |
| Burdick-2010, USA, #521 | <p>Study design: RET, SAS</p> <p>Patients enrolled: 72 (100%)</p> <p>Lost to FU/excluded/missing: NR</p> | <p>Inclusion criteria: 1. Patients without histologic diagnosis were treated only after signs of progression on serial CT and PET/CT studies</p> <p>Exclusion criteria: 1. Patients with recurrent tumors</p> | Stage I: 72 (100%) | <p>Location: NR</p> <p>Histopathology: NOS: 49 (68%)</p> | <p>Age (years): 73 (52-90)</p> <p>Women: NR</p> <p>Race: NR</p> <p>Comorbidities: Inadequate predicted pulmonary reserve after resection; CVD;</p> |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|-------------------------------|---|---|---------------------------|--|--|
| | | | | | cerebrovascular disease (Proportions NR) Performance status: KPS: 80 (40-100) |
| Bush-2004, USA, #535 | Study design: PRO, SAS Patients enrolled: Total: 68 (100%) Medically inoperable: 63 (93%) Refused surgery: 5 (7%) Lost to FU/excluded/missing: NR | Inclusion criteria: 1. Histologic diagnosis of NSCLC 2. Clinical stage 1 disease 3. consent Exclusion criteria: NR | Stage I: 68 (100%) | Location: NR Histopathology: NR | Age (years): Mean: 72 (52-87) Women: 38 (56%) Race: NR Comorbidities: FEV1 Mean (L): 1.15 (0.4–2.1) Performance status: KPS Mean: 65 (50-90) |
| Campeau-2009, Australia, #565 | Study design: RET, SAS Patients enrolled: 34 (100%) Lost to FU/excluded/missing: (See comments) | Inclusion criteria: 1. UICC Stage I histologically or cytologically proven NSCLC treated with or without concomitant chemotherapy. Exclusion criteria: 1. Previous diagnosis of lung cancer 2. Prior treatment for NSCLC 3. Surgery forming part of the initial treatment 4. Evidence of recurrence from a previous cancer. | Stage I: 34 (100%) | Location: NR Histopathology: AC: 13 (38%) SCC: 12 (35%) LCC: 2 (6%) NOS: 7 (21%) | Age (years): 81 (54-88) Women: 14 (41%) Race: NR Comorbidities: SCS: <9: 12 (35%) >9: 21 (62%) NA: 1 (3%) Performance status: ECOG: 0: 3 (9%) 1: 6 (18%) 2: 9 (26%) 3: 2 (6%) NA: 14 (41%) |
| Coon-2008, USA, #803 | Study design: RET, SAS Patients enrolled: Total: 26(100%) | Inclusion criteria: 1. Stage I NSCLC, or residual/recurrent lung cancer after previous treatment, or solitary lung metastases | Stage I: 26 (100%) | Location: Upper: 18 (69%) Middle: 1 (4%) Lower: 6 (23%) Other: 1 (4%) | Age (years): Median: 76.5 Women: NR |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|----------------------------|--|--|----------------------------------|--|--|
| | <p>Medically inoperable: 24 (92%) Refused surgery: 2 (8%)</p> <p>Lost to FU/excluded/missing: NR</p> | <p>Exclusion criteria: NR</p> | | <p>Histopathology: AC: 12 (46%) SCC: 3 (12%) Atypical: 1 (4%) Unknown: 10 (38%)</p> | <p>Race: NR</p> <p>Comorbidities: Total: 24 (92%) COPD: 15 (62%) OMC: 4 (17%) Previous lung surgery: 5 (21%)</p> <p>Performance status: KPS: 65 (60-80)</p> |
| Dunlap-2010, USA, #1032 | <p>Study design: RET, SAS</p> <p>Patients enrolled: Total: 40(100%) Medically inoperable: 37 (92%) Refused surgery: 3 (8%)</p> <p>Lost to FU/excluded/missing: Out of 60, 20 excluded reasons NR.</p> | <p>Inclusion criteria: 1. Patients who have a medically inoperable condition or refused surgery.</p> <p>Exclusion criteria: 1. Patients with abnormal fluorodeoxyglucose (FDG) uptake (maximum standardized uptake value [SUV]>2.5) in the mediastinum</p> | <p>Stage I: 40 (100%)</p> | <p>Location: NR</p> <p>Histopathology: NR</p> | <p>Age (years): 73 (54-87)</p> <p>Women: NR</p> <p>Race: NR</p> <p>Comorbidities: Total: 34 (100%) Poor pulmonary reserve: 26 (76%) CAD: 3 (9%) Cardiac dysfunction (ejection fraction < 30%): 5 (15%)</p> <p>Performance status: KPS < 70%: 3 (8%)</p> |
| Fritz-2008, Germany, #1238 | <p>Study design: RET, SAS</p> <p>Patients enrolled: Total: 40 (100%) Medically inoperable: 37 (92%) Refused surgery: 3 (8%)</p> <p>Lost to FU/excluded/missing: NR</p> | <p>Inclusion criteria: 1. Patients had only one target and no signs of local lymph node metastases or of remote metastases. 2. Karnofsky performance \geq60% and FEV1 > 0.5 L/s (no permanent need of supplemental oxygen). 3. Histological confirmation of NSCLC 4. In case of previous chemotherapy, the time period between chemotherapy and</p> | <p>Stage I: 40 (100%)</p> | <p>Location: Peripheral: 40 (100%)</p> <p>Histopathology: AC: 17(43%) SCC: 8(20%) LCC: 13(32%) NOS: 2 (5%)</p> | <p>Age (years): 74 (59-82)</p> <p>Women: 8 (20%)</p> <p>Race: NR</p> <p>Comorbidities: MI: 7 (18%) CAD: 5 (13%) CHF: 3(8%) CPD: 22(60%)</p> |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|-------------------------------|---|--|--|--|--|
| Graham-2006, Australia, #1403 | Study design: RET, SAS Patients enrolled: Total: 39 (100%) Medically inoperable: 36 (92%) Refused surgery or unknown: 3 (8%) Lost to FU/excluded/missing: 0 | SBRT had to be more than 6 weeks. 5. With reference to stage T2 tumors: tumor size ≤10 cm (largest focus), no involvement of main bronchus, no atelectasis or obstructive pneumonitis, no chest wall involvement Exclusion criteria: 1. Concurrent or adjuvant chemotherapy given Inclusion criteria: 1. Hst confirmed primary clinical stage I NSCLC 2. Medically inoperable or refused surgery Exclusion criteria: NR | Stage I: 39 (100%) | Location: NR Histopathology: SCC: 17 (43%) | PVD: 2 (5%) Diabetes: 4 (10%) Renal disease: 2 (5%) FEV1: 0.66—2.93(median: 1.4 L/s; five patients < 1.0 L/s) Performance status: KPS: 80 % (60%-100%) Age (years): Mean: 72 (53-84) Women: 15 (38%) Race: NR Comorbidities: Respiratory inadequacy: 25 (64%) (FEV 1 < 1.3: 18/25 (72%)) CVD: 6 (15%) >80 years: 2 (5%) Performance status: ECOG > 1: 5 (13%) |
| Iwata-2010, Japan, # 1747 | Study design: NRCS, NR whether data collection was RET or PRO Patients enrolled: Total: 57 (100%) PBRT 80Gy: 20 (35%) PBRT 60 Gy: 37 (65%) Medically Inoperable: Total: 28 (49%) PBRT 80Gy: 10 (34%) PBRT 60 Gy: 19 (66%) Refused surgery: Total: 29 (51%) | Inclusion criteria: 1. Hst confirmed primary NSCLC staged IA or IB 2. Medical inoperability or refusal of surgical resection; 3. WHO performance status ≤2; 4. No history of previous 5. LC; 6. No prior chest RT or chemotherapy; | Total: 57 (100%) Stage 1A: 27(47%) Stage 1B: 30 (57%) PBRT 80Gy: 20 (100%) Stage 1A: 6 (30%) Stage 1B: 14(70%) PBRT 60 Gy: 37 (100%) Stage 1A: 21 (57%) Stage 1B: 16 (43%) | Location: NR Histopathology: Total: 57 (100%) AC: 32 (56%) SCC: 23 (40%) Others: 2 (4%) PBRT 80Gy: 20 (100%) AC: 11 (55%) SCC: 8 (40%) Others: 1 (5%) PBRT 60 Gy: 37 (100%) AC: 21 (57%) | Age: Total: 76 (48-89) PBRT 80Gy: 75 (48-87) PBRT 60 Gy: 78 (57-87) Women: Total: 23 (29%) PBRT 80Gy: 7 (36%) PBRT 60 Gy: 7 (19%) Race: NR Co-morbidities: Total: 28 (100%) Pulmonary: 13 (46%) |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|----------------------------|--|---|---------------------------|---|--|
| | PBRT 80Gy: 10 (34%) PBRT 60 Gy: 19 (66%) Lost to FU/excluded/missing: None | Exclusion criteria: NR | | SCC: 15 (41%) Others: 1 (3%) | CVD: 9 (32%) Severe DM: 5 (18%) Age: 2 (7%) Others: 2 (7%) PBRT 80Gy: 10 (100%) Pulmonary: 7 (70%) CVD: 3 (30%) Severe DM: 1 (10%) Age: 0 Others: 0 PBRT 60 Gy: 18 (100%) Pulmonary: 6 (33%) CVD: 6 (33%) Severe DM: 4 (22%) Age: 2 (11%) Others: 2 (11%) Performance status: NR |
| Jimenez-2010, Spain, #1842 | Study design: RET, SAS Patients enrolled: 47 (100%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. HSt confirmed primary clinical stage I NSCLC 2. Medically inoperable 3. Moderate to good lung function (a forced expiratory volume in 1 s (FEV1) ≥ 30% of predicted value and a carbon monoxide diffusing capacity (DLCO) ≥ 30%). Exclusion criteria: 1. Prior chemotherapy or radiotherapy | Stage I: 47 (100%) | Location: NR Histopathology: NOS: 47 (100%) | Age (years): Mean 68±10 Women: 11 (23%) Race: NR Comorbidities: Mean FEV1: 54±17% Mean CCI score: 2.4±1.3 Performance status: NR |
| Kopek-2009, Denmark, #2040 | Study design: PRO, SAS Patients enrolled: 88 (100%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. HSt confirmed primary clinical stage I NSCLC 2. Medically inoperable 3. Tumor < 6 cm diameter 4. WHO performance status 0-2 | Stage I: 88 (100%) | Location: NR Histopathology: ACC: 30 (34%) SCC: 34 (39%) NOS: 24 (27%) | Age (years): 73 (47-88) Women: 43 (49%) Race: NR Comorbidities: |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|-----------------------------|--|---|---------------------------|---|---|
| | | Exclusion criteria: NR | | | Mean FEV1: 1.06 (0.25-2.60) L CCI score: ≤ 3: 16 (18%) 4: 24 (27%) 5: 25 (28%) ≥6: 23 (26%) Performance status: WHO 0: 15 (17%) 1: 51 (58%) 2: 19 (21%) 3: 2 (2%) |
| Mirri-2009, Italy, #2576 | Study design: PRO, SAS Patients enrolled: 15 (100%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. Medically inoperable 3. Tumor < 5 cm diameter 4. KPS > 70 Exclusion criteria: NR | Stage I: 15 (100%) | Location: Peripheral: 13 (87%) Central: 2 (13%) Histopathology: SCC: 9 (60%) ACC: 2 (13%) | Age (years): 76 Women: NR Race: NR Comorbidities: COPD (number NR) Performance status: KPS > 70 (number NR) |
| Nakayama-2010, Japan, #2684 | Study design: RET, SAS Patients enrolled: Total: 55 (100%) Medically inoperable: 52 (94%) Refused surgery: 3 (6%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. EORTC performance status of 1-2 3. Medically inoperable or refused surgery Exclusion criteria: 1. Existing pleural effusion 2. NSCLC located close to stomach or esophagus | Stage I: 55 (100%) | Location: Lesions: 58 Peripheral: 41 (71%) Central: 17 (29%) 3 patients had a second tumor in contralateral lung Histopathology: ACC: 31 (53%) SCC: 15 (26%) NOS: 4 (7%) LCC: 1 (2%) Undiagnosed: 7 (12%) | Age (years): 74±9 years Women: 14 (26%) Race: NR Comorbidities: Fletcher-Hugh-Jones criteria: I: 7 (13%) II: 9 (16%) III: 32 (58%) IV: 7 (13%) CVD: 8 (14%) |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|---------------------------|--|---|----------------------------|---|---|
| | | | | | Liver/renal: 2 (4%) FEV1 (mL) 818 ± 217 FEV1 (%) 68.2 ± 19.9 Performance status: EORTC criteria: 0: 37 (67%) 1: 16 (29%) 2: 2 (4%) |
| Narayan-2004, USA, #2686 | Study design: PRO, SAS Patients enrolled: 13 (100%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. HSt confirmed primary clinical stage I NSCLC 2. Medically inoperable 3. SWOG performance status 0-2 Exclusion criteria: 1. Prior thoracic RT | Stage I: 13 (100%) | Location: NR Histopathology: NOS: 13 (100%) | Age (years): Mean 67±18 (calculated) Women: 1 (9%) (calculated) Race: NR Comorbidities: NR Performance status: NR |
| Nyman-2006, Sweden, #2750 | Study design: PRO, SAS Patients enrolled: 45 (100%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. Medically inoperable Exclusion criteria: 1. Tumor diameter > 5 cm 2. Central tumor with extension close to trachea, main bronchus, or esophagus | Stage I: 45 (100%) | Location: NR Histopathology: SCC: 18 (40%) ACC: 15 (33%) NOS: 3 (7%) | Age (years): Mean 74 (58-84) Women: 20 (44%) Race: NR Comorbidities: Mean FEV1: 1.3 (0.7-2.7) Poor lung function: 31 (69%) CVD: 24 (53%) Other serious malignancies: 6 (13%) Performance status: KPS: Mean 80 (60-100) |
| Olsen-2011, USA, #2792 | Study design: RET, SAS Patients enrolled: | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. Single lesion | Stage I: 130 (100%) | Location: Peripheral: 115 (88%) Central: 15 (12%) | Age (years): 75 (31-92) Women: |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|--------------------------------|---|---|---|---|--|
| | Total: 130 (100%) Medically inoperable: 117 (90%) Refused surgery: 13 (10%) Lost to FU/excluded/missing: 0 | 3. No prior malignancy for prior 2 years 4. Prescribed SBRT dose: 18Gy in 3, 9 Gy in 5, or 10 Gy in 5 frs 5. FU duration > 3 months Exclusion criteria: 1. Nodal or metastatic disease | | Histopathology: Hst confirmed: 110 (85%) Undiagnosed: 20 (15%) NR | 65 (50%) Race: NR Comorbidities: NR Performance status: NR |
| Palma-2011, Netherlands, #2843 | Study design: PRO, SAS Patients enrolled: Total: 176 Medically inoperable: 169 (96%) Refused surgery or NR: 7 (4%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. Severe COPD or ventilatory impairment 3. Medically inoperable or refused surgery Exclusion criteria: NR | Stage I: 176 (100%) (16 Patients had a second primary T1 tumor treated synchronously) | Location: NR Histopathology: Hst confirmed: 57 (32%) Histology NR | Age (years): 70 (47-86) Women: 79 (45%) Race: NR Comorbidities: COPD: GOLD III: 133 (76%) GOLD IV: 43 (24%) FEV1: median 0.94 (0.36-1.99) L CCI score: median 4 (2-9) Performance status: NR |
| Pennathur-2007, USA, #2896 | Study design: RET, SAS Patients enrolled: 19 (100%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. Medically inoperable 3. Peripheral tumor ≤ 4 cm diameter Exclusion criteria: 1. Central tumor | Stage I: 19 (100%) | Location: Peripheral: 19 (100%) Histopathology: SCC: 8 (42%) ACC: 8 (42%) NOS: 3 (16%) | Age (years): Median 78 (68-88) Women: 11 (58%) Race: NR Comorbidities: Median CCI: 4 (3-12) Poor pulmonary function: 10 (53%) Increased cardiac risk: 7 (37%) Multiple comorbidities: 8 (42%) |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|------------------------------|---|--|---------------------------|--|--|
| | | | | | Mean FEV1: 0.73 ± 0.21 Performance status: NR |
| Pennathur-2009, USA, #2898 | Study design: RET, SAS Patients enrolled: 21 (100%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. Medically inoperable Exclusion criteria: NR | Stage I: 21 (100%) | Location: NR Histopathology: SCC: 8 (38%) ACC: 6 (29%) NOS: 6 (29%) Not determined: 1 (5%) | Age (years): 71 (61-85) Women: 12 (57%) Race: NR Comorbidities: Median CCI: 5 (0-10) Median FEV1: 0.67 (0.5 0.86) L Median DLCO: 30% (19 58%) Median CCI: 5 (0-10) Cardiac risk: 6 (29%) Multiple: 8 (38%) Performance status: NR |
| Ricardi-2010, Italy, #3098 | Study design: PRO, SAS Patients enrolled: Total: 62 (100%) Medically inoperable: 56 (90%) Refused surgery: 6 (10%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Primary clinical stage I NSCLC < 5 cm diameter 2. Medically inoperable or refused surgery 3. ECOG performance status < 2 4. No prior RT at site of SBRT Exclusion criteria: 1. Lesions located < 2 cm from airways or < 1 cm from major blood vessels | Stage I: 62 (100%) | Location: NR Histopathology: ACC: 13 (20%) SCC: 14 (23%) LCC: 3 (5%) BAC: 1 (2%) NOS: 9 (14%) | Age (years): Mean 74 (53-83) Women: 10 (16%) Race: NR Comorbidities: COPD: 31 (50%) CVD: 15 (24%) Elderly: 10 (16%) Performance status: ECOG < 2 |
| Scorsetti-2007, Italy, #3362 | Study design: SAS (unclear if PRO or RET) Patients enrolled: 43 (100%) Lost to FU/excluded/missing: | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. Medically inoperable Exclusion criteria: 1. Tumor diameter > 5.5 cm | Stage I: 43 (100%) | Location: Right upper lobe: 18 (39%) Right lower lobe: 8 (17%) Right hilum: 2 (4%) Left upper lobe: 11 (24%) Left lower lobe: 4 (9%) Left hilum: 3 (7%) | Age (years): 76 (52-90) Women: 9 (21%) Race: |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|------------------------------|--|---|----------------------------|---|---|
| | 0 | 2. Central tumor growth < 2 cm to the trachea, main bronchus or esophagus 3. Prior chemotherapy | | Histopathology: Lesions: 43 ACC: 9 (21%) SCC: 12 (28%) BAC: 5 (12%) NOS: 14 (33%) Mixed: 1 (2%) | NR Comorbidities: COPD: 24 (56%) Age (years)/CVD: 19 (44%) Performance status: ECOG 0: 29 (21%) 1: 9 (67%) 2: 5 (12%) |
| Shibamoto-2012, Japan, #4629 | Study design: PRO, SAS Patients enrolled: Total: 180 (100%) Medically inoperable: 120 (67%) Refused surgery: 60 (33%) Lost to FU/excluded/missing: 0 | Inclusion criteria: Histologically proven NSCLC stage 1 not suitable for surgery for medical or functional reasons Exclusion criteria: 1. Tumor > 5 cm in greatest dimension 2. WHO PS < 2 or PS 3 when not due to pulmonary disease 3. Active concurrent cancer 4. FEV1/FVC < 60% or percentage vital capacity < 75% | Stage I: 120 (100%) | Location: Not stated by operability Histopathology: Pathological confirmation: 120 (100%) Not stated by operability | Age (years): 77 (29-89) all cases Women: 57 (32%) all cases Race: NR Comorbidities: NR Performance status: WHO 0: 87 (48%) 1: 69 (38%) 2: 21 (12%) 3: 3 (2%) all cases |
| Song-2009, Korea, #3549 | Study design: PRO, SAS Patients enrolled: Total: 32 (100%) Medically inoperable: 31 (97%) Refused surgery: 1 (3%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Pathologically confirmed NSCLC 2. Primary clinical stage I NSCLC 3. Medically inoperable or refused surgery 4. Tumor < 5 cm in diameter 5. ECOG performance status < 2 Exclusion criteria: Recurrent or new primary lung cancer with prior history of lung | Stage I: 32 (100%) | Location: Peripheral: 23 (72%) Central: 9 (28%) Histopathology: SCC: 18 (56%) ACC: 11 (34%) NOS: 3 (9%) | Age (years): 72 (58-89) Women: 6 (19%) Race: NR Comorbidities: Poor lung function: 20 (62%) (Median FEV1: 1.06 L) Other medical problem: 7 (22%) Age (years) > 80 years: 4 |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|----------------------------|--|--|---|--|--|
| | | cancer | | | (12%) Performance status: ECOG 1: 21 (66%) 2: 11 (34%) |
| Stephans-2009, USA, #3614 | Study design: RET (registry) Patients enrolled: 86 (100%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. Medically inoperable Exclusion criteria: NR | Stage I patients: 86 (100%) Stage I lesions: 94 (100%) | Location: NR Histopathology: SCC: 32 (34%) ACC: 15 (16%) PD/other: 14 (15%) No diagnosis: 33 (35%) | Age (years): 73 (40-90) Women: 48 (56%) Race: NR Comorbidities: Pulmonary: 69 (73%) Cardiac: 15 (16%) Other/multiple: 10 (11%) CHF: 41 (48%) Performance status: KPS: 80 (40-90) |
| Taremi-2011, Canada, #3732 | Study design: PRO, SAS Patients enrolled: 108 (100%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. Medically inoperable Exclusion criteria: NR | Stage I: 108 (100%) | Location: 114 lesions Right upper lobe: 38 (33%) Right middle lobe: 10 (9%) Right lower lobe: 18 (16%) Left upper lobe: 31 (27%) Left lower lobe: 17 (15%) Histopathology: Lesions: 114 ACC: 34 (30%) SCC: 22 (19%) LCC: 6 (5%) NOS: 19 (17%) Undiagnosed: 33 (29%) | Age (years): Mean 73 (48-90) years Women: 55 (51%) Race: NR Comorbidities: NR, medical inoperability assessed by an experienced thoracic surgeon and/or a multidisciplinary tumor board Performance status: NR |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|----------------------------|--|---|---|--|--|
| Takeda-2009, Japan, #3700 | <p>Study design: RET, SAS</p> <p>Patients enrolled: Total: 63 (100%) Medically inoperable: 49 (78%) Refused surgery: 14 (22%)</p> <p>Lost to FU/excluded/missing: 0</p> | <p>Inclusion criteria: 1. Primary clinical stage I NSCLC</p> <p>2. WHO performance status ≤ 2</p> <p>Exclusion criteria: 1. Prior radiation to lung or mediastinum</p> | Stage I: 63 (100%) | <p>Location: NR</p> <p>Histopathology: Hst confirmed: 52 (82%) ACC: 35 (56%) SCC: 14: 22% NOS: 3 (5%) Undiagnosed: 11 (18%)</p> | <p>Age: 78 (56-91)</p> <p>Women: 23 (36%)</p> <p>Race: NR</p> <p>Co-morbidities: COPD, advanced age, other illnesses: 49 (78%)</p> <p>Performance status: WHO ≤ 2: 63 (100%)</p> |
| Turzer-2011, Norway, #3842 | <p>Study design: RET, SAS</p> <p>Patients enrolled: Total: 36 (100%) Medically inoperable: 35 (97%) Refused surgery: 1 (3%)</p> <p>Lost to FU/excluded/missing: 0</p> | <p>Inclusion criteria: 1. Pathologically confirmed NSCLC or PET positive pulmonary lesion with evidence of growth evaluated by at least 2 consecutive CT scans</p> <p>2. Primary clinical stage I NSCLC</p> <p>3. Medically inoperable or refused surgery</p> <p>4. Tumor < 6 cm diameter</p> <p>5. Tumor located > 2 cm from main bronchus</p> <p>6. ECOG performance status 0-4</p> <p>Exclusion criteria: NR</p> | <p>Stage I: 35 (100%) (Total of 38 Lesions)</p> | <p>Location: NR</p> <p>Histopathology: Hst confirmed: 28 lesions (74%) ACC: 17 (45%) SCC: 10 (26%) LCC: 1 (3%) Undiagnosed: 10 (26%)</p> | <p>Age (years): 74 (54-85)</p> <p>Women: 23 (64%)</p> <p>Race: NR</p> <p>Comorbidities: Median FEV1: 1.4 (0.4-4.5) CVD: 32 (89%)</p> <p>Performance status: ECOG: 0: 3 (8%) 1: 9 (25%) 2: 18 (50%) 3: 8 (22%)</p> |
| Vahdat-2010, USA, #3864 | <p>Study design: PRO, SAS</p> <p>Patients enrolled: 20 (100%)</p> <p>Lost to FU/excluded/missing: 0</p> | <p>Inclusion criteria: 1. Hst confirmed primary clinical stage I NSCLC</p> <p>2. Medically inoperable</p> <p>Exclusion criteria: 1. Pure BAC</p> | Stage I: 20 (100%) | <p>Location: NR</p> <p>Histopathology: ACC: 8 (40%) ACC: 5 (25%) NOS: 7 (35%)</p> | <p>Age (years): Mean 75 (64-86)</p> <p>Women: 16 (80%)</p> <p>Race: NR</p> <p>Comorbidities: Mean FEV1: 1.12 (0.53)</p> |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|--|--|--|--------------------|--|--|
| van der Voort van Zyp-2009, Netherlands, #3885 | Study design: SAS, unclear if PRO or RET Patients enrolled: Total: 70 (100%) Medically inoperable: 65 (93%) Refused surgery: 5 (7%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. Medically inoperable or refused surgery 3. Peripheral tumor > 2 cm from trachea and main bronchus Exclusion criteria: NR | Stage I: 70 (100%) | Location: NR Histopathology: LCC: 16 (44%) SCC: 11 (31%) ACC: 7 (19%) NOS: 2 (6%) Unknown: 34 (49%) | 2.48) FEV1 < 40% DLCO < 40% Performance status: NR Age (years): 76 (54-90) Women: NR Race: NR Comorbidities: CCI score: ≥ 4: 5 (7%) 3-4: 31 (44%) 1-2: 32 (46%) 0: 2 (3%) Median FEV1: 1.38 (0.81 3.81) |
| Videtic-2010, USA, #3958 | Study design: RET, SAS Patients enrolled: 26 (100%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. Medically inoperable Exclusion criteria: NR | Stage I: 26 (100%) | Location: Peripheral: 25 (89%) Central: 3 (11%) Histopathology: Lesions: 28 NOS: 20 (71%) | Age (years): 74 (49-88) Women: 13 (50%) Race: NR Comorbidities: Median FEV1: 1.26 (0.62 2.41) Median Charlson score: 3 (0-8) Pulmonary: 20 (77%) Cardiac: 4 (15%) Multiple: 2 (8%) Performance status: Median KPS: 70 (40-100) |

Values are presented as median (range) unless otherwise noted.

Appendix Table C2. Outcomes and interventions of studies that address Key Question 1

| Study | Study Outcomes | Interventions |
|-----------------------------------|--|--|
| <p>Andratschke 2011, #132</p> | <p>Study Objective: To report patterns of failure of SBRT in inoperable patients with histologically confirmed stage I NSCLC</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of Outcome(s): OS, CSS, LCT, Toxicity</p> <p>Cause of death: Dead: 59 (64%) Dead due to LC: 25 (42%) Dead due to concurrent disease: 29 (49%) Cause of death NR: 5 (8%)</p> <p>Length of FU: 21 (3-87) months</p> | <p>Intervention name: SBRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: Hypofractionated SBRT Total dose: 24-45 Gy to 60% isodose line of PTV in 3-5 frs for 5-12 days Total dose given at 60% isodose line (Gy): 37.5 (24-45) Dose given per fraction (Gy): 12.5 (5-15) No. of frs given: 3 (3-7)</p> <p>Technical details: None</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • All time intervals were calculated from the last day of SBRT • During Rx, Patients monitored daily for acute Rx toxicity. Thereafter, follow-up visits at 4-6 weeks and 4, 7, and • 12 months and then at 6 month intervals. • FU investigations included lung function test and CT thorax. • Acute toxicity: CTCAE v3.0 criteria during and up to 3 months after RT. • Late toxicity: RTOG/EORTC criteria. |
| <p>Baumann-2006, #271</p> | <p>Study Objective: To review results of SBRT treatment of 138 Patients with medically inoperable stage I NSCLC treated during 1996 - 2003 at five different centers in Sweden and Denmark.</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of Outcomes: LCT, OS, CSS, Toxicity</p> <p>Cause of death: Dead: 91 (66%)</p> | <p>Intervention name: SBRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: 10 to 20 Gy X 2-4 frs given 2 to 3 days apart. Total dose: 30-48 Gy, 65% isodose at the periphery of PTV</p> <p>Technical details: 3D planning Linear accelerator delivered at 6-MV</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Response is based on CT-scans performed in a period of 0.589.3 months (median 16.3) post therapy, and should therefore be regarded as “best |

| Study | Study Outcomes | Interventions |
|---------------------------|---|--|
| | <p>Dead due to concurrent disease: 55 (60%) Cause of death NR: 36 (40%)</p> <p>Length of FU: 33 (1-107) months</p> | <p>response.”</p> <ul style="list-style-type: none"> • Toxicity evaluated according to RTOC criteria |
| <p>Baumann-2009, #270</p> | <p>Study Objective: To evaluate the impact of COPD and CVD on Patients treated in this phase II study, subjective toxicity data were registered during follow-up and compared to the objective data of spirometry evaluations, CT-scans and dosimetric data (#269).</p> <p>Primary outcome: Progression-free survival at 36 months</p> <p>Definition: NR</p> <p>Secondary outcome(s): LCT, OS, Toxicity</p> <p>Definitions: NR</p> <p>Cause of death: Dead: 27 (47%) Dead due to LC: 7 (26%) Dead due to concurrent disease: 18 (67%) Cause of death unknown: 2 (7%)</p> <p>Length of FU: Median: 35 months (4-47)</p> | <p>Intervention name: SBRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: 15 Gy in 3 frs (total dose of 45 Gy) at the 67% isodose of the PTV. BED: 112 Gy. Rx was given every second day.</p> <p>Technical details: 3DCT planning Linear accelerator delivered at 6-MV</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Clinical, pulmonary and radiological evaluations- 6 weeks, 3, 6, 9, 12, 18, and 36 months post SBRT. • Median FU time was calculated from date of registration to date of last visit • Toxicity CTCAE version 2 • Radiation-related pulmonary fibrosis >90 days post-Rx, RTOG/EORTC Late Radiation Morbidity Scoring Scheme-Lung was used • FEV1 was graded according to the GOLD criteria • Early toxicity defined as ≤ 18 months. Late toxicity defined as > 18 months |
| <p>Bogart-2010, #382</p> | <p>Study Objective: To define the maximally accelerated course of conformal radiotherapy and to describe the short-term and long-term toxicity of therapy.</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of outcomes: OS, LCT, Toxicity</p> | <p>Intervention name: 3DRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: Daily radiation fraction size was escalated and the number of frs reduced. Total nominal radiotherapy dose maintained at 70 Gy throughout each course. Treatment administered on consecutive weekdays. Range N of frs: (17 – 29) Range fraction size (Gy): (2.41-4.11) Range N of weeks: (3.4 – 5.8)</p> <p>Technical details: 3D planning</p> |

| Study | Study Outcomes | Interventions |
|----------------------------------|--|--|
| | <p>Cause of death: NA</p> <p>Length of FU: 53 (35-61) months</p> | <p>Beam energy: (4 -25) MV 83% treated with 6MV photons</p> <p>Treatment Intention: NR</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Overall survival was defined as the time between protocol registration and death • Toxicity was assessed using the NCI CTC (version 2.0) • Patients were assessed weekly during therapy. Patients were assessed 3 weeks, 6 weeks, and 3 months after the completion of therapy, then at least every 3 months for 2 years, and then every 6 months for 3 years. • Evaluation by a thoracic surgeon (for suitability for lobectomy) was mandated if criteria for pulmonary dysfunction were not met, |
| <p>Bollineni-2012, #4548</p> | <p>Study Objective: To investigate the prognostic value of FDG-PET uptake at 12 weeks after SBRT for stage I NSCLC</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of Outcome(s): OS, CSS, LCT</p> <p>Cause of death: Dead: 29 (22%) Dead due to LC: 13 (45%) Dead due to concurrent disease: 16 (55%)</p> <p>Length of FU: 17 (3-40) months</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Novalis-BrainLAB system (Westchester, IL)</p> <p>Dose/frequency/details: Hypofractionated SBRT Total dose: 60 Gy to 90% isodose line of PTV in 3-8 frs for 5-12 days</p> <p>Technical details: 4-D CT planning</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria: NR</p> |
| <p>Bradley-2003, #445</p> | <p>Study Objective: To review the outcome for 56 Stage I non-small-cell lung cancer treated definitively with three dimensional conformal radiotherapy (3D-CRT) and to investigate the value of elective nodal irradiation in this patient population.</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> | <p>Intervention name: 3DRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: 60–69 Gy: 7 (13%) 70 Gy: 23 (42%) >70 Gy: 25 (45%) Median isocenter dose: 70 Gy (59.94 - 83.85), frs of 1.8 or 2 Gy, given 5 days weekly within 6 – 8 weeks.</p> |

| Study | Study Outcomes | Interventions |
|--------------------|--|--|
| | <p>Definitions: NA</p> <p>List of outcomes: OS, LCT, Toxicity</p> <p>Cause of death: NA</p> <p>Length of FU: 20 (6 – 72) months</p> | <p>Twenty-two patients received RT directed to elective regional lymphatics in doses of 45–50 Gy</p> <p>Technical details: 3D planning</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • RTOG criteria used to evaluate toxicity grade 1-5 patients were followed at 3-month intervals for the first 2 years and at 6-month intervals thereafter. • Evaluations at the time of follow-up consisted of a history and physical examination. Chest radiographs were done at 3- or 6-month intervals for the first 2 years. CT scans of the chest were typically done 6 and 12 Months after treatment completion and thereafter only when clinically indicated. • Patients who had an initial radiographic response to treatment and a stable mass at each follow-up visit were considered to have local control. • Patients were considered to have local failure only if clinical, radiographic, or biopsy evidence of progression was observed |
| Burdick-2010, #521 | <p>Study Objective: To determine whether the pretreatment SUVmax from the staging FDG PET/CT could predict for mediastinal failure, distant metastases, and OS in medically inoperable patients treated with SBRT for early-stage NSCLC. To “define the maximal accelerated course of therapy”</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of outcomes: OS, LCT</p> <p>Cause of death: Dead: 30 (42%) Dead due to LC: 13 (43%) Dead due to concurrent disease: 14 (47%) Causes of death unknown: 3 (10%)</p> <p>Length of FU: 16.9 (0.1 – 37.9) months</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Novalis-BrainLAB system (Westchester, IL)</p> <p>Dose/frequency/details: Total dose: 60 Gy (20 Gy X 3): 26 (36%) 50 Gy (10 Gy X 5): 40 (56%) 50 Gy (5 Gy X 10): 8 (11%)</p> <p>Technical details: 3D planning 6-MV photons</p> <p>Treatment Intention: NR</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Patients were followed every 3 Months with clinical examination and CT scan of the chest. Pulmonary function testing was done at 6-month intervals. Post-treatment PET scans were only performed to evaluate possible recurrences and are not included in this analysis. • Local failure was dated from the initial CT abnormality. Local failure was defined as increasing lesion size on two consecutive CT scans, confirmed by serial PET imaging with or without positive biopsy for carcinoma. |
| Bush-2004, #535 | <p>Study Objective:</p> | <p>Intervention name:</p> |

| Study | Study Outcomes | Interventions |
|--------------------|--|---|
| | <p>To determine the efficacy and toxicity of high-dose hypofractionated PBRT for Patients with clinical stage I lung cancer.</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of Outcomes: CSS, LCT, OS, Acute Toxicity</p> <p>Cause of death: NR</p> <p>Length of FU: Median: 30 months</p> | <p>PBRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: 51 CGE in 10 equally divided frs over 2-weeks: 22 (32%) 60 CGE in 10 frs over 2-weeks: 46 (68%)</p> <p>Technical details: Hypofractionated 3D planning Linear accelerator delivered at 6-MV</p> <p>Treatment Intention: NR</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Patients received clinical evaluation every 3 months for the first year, then every 6 months, then annually after the fifth year. • Chest CT scans to determine tumor status were done at 3-month intervals up to 1 year after treatment, then every 6 months, and annually after the fifth year of follow-up. • Patients were monitored weekly for acute toxicity during treatment. |
| Campeau-2009, #565 | <p>Study Objective: To review retrospectively disease control and survival in patients with Stage I NSCLC patients who were treated with chemoradiotherapy or RT between 2000 and 2005.</p> <p>Primary outcome: OS</p> <p>Definition: OS was measured from treatment starting date to the date of death, regardless of the cause of death</p> <p>Secondary outcome(s): LCT, Distant LCT, and PFS</p> <p>Definitions: NR for LCT</p> <p>List of outcomes: OS, LCT</p> <p>Cause of death: NR</p> <p>Length of FU: NR</p> | <p>Intervention name: 3DRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: 60 Gy X 30 frs over 6 weeks: 23 (68%) Hypofractionated dose: 50-55 Gy X 20 frs over 4 weeks: 11 (32%)</p> <p>The hypofractionated regimen was used only in cases in which the mediastinum and spinal cord were not included in the treatment volume.</p> <p>Technical details: ≥6-MV photons</p> <p>Treatment Intention: NR</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Patients were seen every 3 months after completion of treatment for the first 2 years. The interval was usually increased to every 6 months provided there was no evidence of recurrence. • Chest X-ray or CT scan of the chest and upper abdomen were performed before each visit in most cases. An F-18 FDG PET scan was performed in case of equivocal CT scan results |

| Study | Study Outcomes | Interventions |
|--------------------|---|---|
| Coon-2008, #803 | <p>Study Objective: To assess the outcomes of Patients treated with stereotactic body radiation therapy (SBRT) in Patients with primary, recurrent, or metastatic lung lesions, with a focus on positron emission tomography (PET)/computed tomography (CT)-based management.</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of Outcomes: LCT, OS</p> <p>Cause of death: NR</p> <p>Length of FU: Median: 12 months</p> | <ul style="list-style-type: none"> Local progression of (LCT) was defined per the RECIST criteria Local PFS was not censored by distant progression <p>Intervention name: SBRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: 60 Gy X 3 frs prescribed to the 80% isodose line</p> <p>Technical details: CyberKnife® Robotic Radiosurgery System with Synchrony™ Linear accelerator delivered at 6-MV</p> <p>Treatment Intention: NR</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> All Patients received regularly scheduled follow-up with planned CT or PET-CT imaging per standard protocol. Local control was defined in our study as the lack of disease progression or reduction of standardized uptake value (SUV) at the site treated on follow-up imaging. |
| Dunlap-2010, #1032 | <p>Study Objective: The purpose of this study was to compare the outcomes and local control rates of Patients with peripheral T1 and T2 non-small-cell lung cancer treated with stereotactic body radiation therapy.</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of Outcomes: LCT, OS, Toxicity</p> <p>Cause of death: No treatment related deaths occurred</p> <p>Length of FU: 12.5 (2-35) months</p> | <p>Intervention name: SBRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: Median prescribed dose: 60 Gy (30-60 Gy) in 3 to 5 frs Median BED: 150 Gy (78-180 Gy)</p> <p>Technical details: 3D planning</p> <p>Treatment Intention: NR</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> After SBRT, followup was performed approximately 4 to 8 weeks after treatment and approximately every 3 months thereafter. CT of the chest was routinely obtained at 3-month intervals from the completion of radiotherapy. PET-CT was not routinely obtained before the initiation of therapy. Toxicity was graded using CTCAE version 3.0 Local tumor recurrence was defined as a 20% increase in the largest tumor |

| Study | Study Outcomes | Interventions |
|--------------------|---|--|
| Fritz-2008, #1238 | <p>Study Objective: To review response rates, local control, survival and side effects after nonfractionated stereotactic high single-dose body radiation therapy for lung tumors.</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of Outcomes: LCT, OS, Lung function, Toxicity</p> <p>Cause of death: Dead: 18 (45%) Dead due to LC: 13 (72%) Dead due to concurrent disease: 5 (28%)</p> <p>Length of FU: 20 (6-61.5) months</p> | <p>diameter on successive follow-up imaging at 3-month intervals based on RECIST.</p> <ul style="list-style-type: none"> Local recurrences were demonstrated by an increase in abnormal FDG uptake required to correspond to an enlarging CT abnormality. Follow-up was determined from the date of the final SBRT treatment. Guidelines for inoperability were determined by the thoracic surgeon and typically included a predicted postoperative forced expiratory volume in 1 second of less than 30%, severely reduced diffusion capacity greater 40% predicted, a performance status of 3 or greater, or severe cardiac disease. <p>Intervention name: SBRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: BED 90% isodose: 99.9 Gy</p> <p>Technical details: 4D Planning</p> <p>Treatment Intention: NR</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> All of the Patients were checked using high-resolution helical CT scans of the entire lung at 6 and 12 weeks after the single-dose radiation treatment. For all Patients further CT scan follow-up examinations then took place in 3-month intervals. The follow-up periods for overall and lung cancer specific survival were defined as the time between irradiation and the last contact (censored) or death. No patient dropped out of follow-up. This means all Patients could be observed until the date of evaluation or the occurrence of an event. RTOG criteria used to evaluate toxicity |
| Graham-2006, #1403 | <p>Study Objective: To review results of radical radiotherapy with 3DRT in Sydney to inform Patients contemplating treatment options for early stage NSCLC.</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> | <p>Intervention name: 3DRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: Prescribed dose: 65 Gy 35 frs using concurrent end-phase boost 5 weeks</p> <p>Technical details: 3D Planning Delivered: 45 Gy in 25 frs plus 20 Gy in 10 frs concurrently during the last 2</p> |

| Study | Study Outcomes | Interventions |
|---------------------|--|---|
| | <p>Definitions: NA</p> <p>List of outcomes: OS, CSS, toxicity</p> <p>Cause of death: Dead: 22 (56%) Dead due to LC: 12 (55%) Dead due to concurrent disease: 10 (45%)</p> <p>Length of FU: Mean 40 (11-88) months</p> | <p>weeks of treatment, with a 6-hour interfraction interval</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria: NR</p> |
| Iwata-2010, #1747 | <p>Study Objective: To analyze the safety and efficacy of high-dose proton therapy and carbon-ion therapy applied to stage I NSCLC</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of Outcome(s): OS, DSS, Local control, Toxicity</p> <p>Cause of death: NR</p> <p>Length of FU: All patients observed for a minimum of 1.5 years or until death. Median duration of follow-up was 35.5 (18-66) months for living pts & 30.5 (4-66) months for all pts.</p> | <p>Intervention name: PBRT</p> <p>Vendor name: Synchrotron (Mitsubishi Electric Corporation, Kobe, Japan) 3-D Rx planning system ((FOCUS-M, CMS, St. Louis, Mo and Mitsubishi Electric Corporation)</p> <p>Dose/frequency/details: PBRT 80Gy: 20 fractions, BED 10(Gy): 112</p> <p>PBRT 60 Gy: 10 fractions BED 10(Gy): 96</p> <p>Technical details: Pts were treated with 150-MeV proton beams</p> <p>Treatment Intention: NR</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • After Rx, pts FU at 1.5, 3, 4.5, 6, 9, and 12 months during the 1st yr, at intervals of 3 months in the 2nd yr, and at 6-month intervals in the 3rd yr. • CT, tumor marker, Brain MRI and FDG-PET were used to monitor tumor progression. • Local responses was assessed according to the modified WHO response evaluation criteria. • Toxicities were evaluated with the CTCAE version 3.0. • Medically inoperability defined as pts with poor pulmonary function (vital capacity <75% or ratio of FEV 1 to forced vital capacity <60%), a history of major CVD, severe DM, advanced age (80 years old), or other debilitating conditions that preclude surgery. |
| Jimenez-2010, #1842 | <p>Study Objective: To assess clinical outcomes of high-dose accelerated 3DRT in medically</p> | <p>Intervention name: 3DRT</p> |

| Study | Study Outcomes | Interventions |
|---|---|--|
| | <p data-bbox="312 131 821 155">inoperable patients with primary stage I NSCLC</p> <p data-bbox="312 185 516 237">Primary outcome: NR</p> <p data-bbox="312 266 432 318">Definition: NA</p> <p data-bbox="312 347 579 399">Secondary outcome(s): NR</p> <p data-bbox="312 428 432 480">Definition: NA</p> <p data-bbox="312 509 512 561">List of outcomes: OS</p> <p data-bbox="312 591 495 643">Cause of death: NR</p> <p data-bbox="312 672 470 724">Length of FU: 36 months</p> | <p data-bbox="1142 155 1913 261">Vendor name: XiO treatment planning system, Computer Medical System, Inc. Linear accelerator: Elekta SL15, Elekta, Crawley, OK, or Siemens Oncor, Siemens Medical Solutions, Concord, CA</p> <p data-bbox="1142 293 1986 375">Dose/frequency/details: Individual dose-escalation scheme to maximal allowed total tumor dose of 79Gy in twice daily (BID) frs of 1.8 Gy with interfraction interval of at least 8 hours</p> <p data-bbox="1142 404 1339 485">Technical details: 3D planning Beam energy NR</p> <p data-bbox="1142 514 1373 566">Treatment Intention: Curative</p> <p data-bbox="1142 596 2003 899">Follow-up and Evaluation Criteria:</p> <ul data-bbox="1142 626 2003 899" style="list-style-type: none"> • Survival status of the patients (alive or dead by any cause) was evaluated in July 2009 in both series of cases • Follow-up was done by the Pulmonologist and/or Radiation Oncologist according to the national guidelines. Survival was updated using the “Gemeentelijke Basis Administratie” system, a decentralized population registration system containing information about all inhabitants of The Netherlands. • During radiation treatment, patients were seen weekly by the Radiation Oncologist to treat the radiation-related complaints. (Details of complaints not specified) |
| <p data-bbox="86 907 233 959">Kopek-2009, #2040</p> | <p data-bbox="312 907 1073 989">Study Objective: To determine the prognostic role of co-morbidity in medically inoperable patients with stage I NSCLC treated with SBRT</p> <p data-bbox="312 1018 516 1070">Primary outcome: NR</p> <p data-bbox="312 1099 432 1151">Definition: NA</p> <p data-bbox="312 1154 579 1206">Secondary outcome(s): NR</p> <p data-bbox="312 1235 432 1287">Definition: NA</p> <p data-bbox="312 1317 554 1369">List of outcomes: OS, CSS, LCT, toxicity</p> <p data-bbox="312 1398 495 1450">Cause of death: NR</p> | <p data-bbox="1142 907 1356 959">Intervention name: SBRT</p> <p data-bbox="1142 989 1803 1094">Vendor name: Treatment planning system: MDS_Nordion, Freiburg, Germany Helax-TMS CadPlan Plus/Eclipse, Varian Medical Systems, Palo, Alto, CA</p> <p data-bbox="1142 1123 1766 1205">Linear accelerator: Siemens Primus, Siemens Medical Solutions, Concord, CA Varian Clinac 2100/2300</p> <p data-bbox="1142 1234 1719 1339">Dose/frequency/details: Prescribed dose: 45 or 68 Gy to PTV 95% isodose line 3 frs 5-8 days</p> <p data-bbox="1142 1369 1415 1421">Technical details: Beam energy 6- or 8-MeV</p> <p data-bbox="1142 1450 1373 1474">Treatment Intention:</p> |

| Study | Study Outcomes | Interventions |
|-------------------------|--|--|
| | Length of FU: 44 (2-96) months | Curative Follow-up and Evaluation Criteria: <ul style="list-style-type: none"> • Clinical FU and CT scan at 3, 6, 9, 12, 24 months then annually after SBRT • Toxicity assessed according to CTCAE v.3.0 criteria; Only deteriorations from baseline were registered as adverse events. |
| Mirri-2009, #2576 | Study Objective: To report on the clinical outcome of hypofractionated conformal radiotherapy for medically inoperable stage I NSCLC < 5 cm in diameter Primary outcome: NR Definition: NA Secondary outcome(s): NR Definition: NA List of outcomes: OS, LCT, toxicity Cause of death: Dead: 7 (47%) Length of FU: 25 (4-46) months | Intervention name: 3DRT Vendor name: Treatment planning system: ECLIPSE,v.6.2, Varian Associates, Palo Alto, CA Pinnacle. V.7.4f, Philips Medical System, Best, Netherlands Dose/frequency/details: Prescribed dose: 40 Gy to the PTV 95% isodose line BED: 72 Gy 5 frs 2.5 weeks Technical details: Beam energy 6-MeV Treatment Intention: Curative Follow-up and Evaluation Criteria: <ul style="list-style-type: none"> • CT scan at 4 months after 3DRT, then every 4 months thereafter • Acute toxicity assessed according to RTOG criteria Late toxicity assessed according to EORTC and CTCAE v.2.0 Data also evaluated by ECOG CTC criteria (both late and acute) |
| Nakayama-2010, #2684 | Study Objective: To evaluate the role of PBT for Patients with medically inoperable stage I NSCLC Primary outcome: NR Definition: NA Secondary outcome(s): NR Definition: NA List of outcomes: | Intervention name: PBT Vendor name: PROBEAT, Hitachi, Tokyo Dose/frequency/details: Central Lesions: 73 GyE in 22 frs: 17 (29%) Peripheral Lesions: 66 GyE in 10 frs: 41 (71%) BED: 1.1 Technical details: Beam energies 155-250 MeV Treatment Intention: Curative |

| Study | Study Outcomes | Interventions |
|--------------------------------|--|---|
| | <p>OS, LCT, toxicity</p> <p>Cause of death: Dead due to LC: 0 Dead due to concurrent disease: 2 (4%)</p> <p>Length of FU: 18 (1.4-53) months</p> | <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Monthly at completion of PBT for 6 months • Chest CT every 3 months for 2 years after PBT Spirometry • Toxicity scored according to CTCAE v3.0 • The local control rate for 58 tumors was calculated to the date of tumor size increase of >20%. • Survival rates were calculated from the first day of treatment with PBT |
| <p>Narayan-2004, #2686</p> | <p>Study Objective: To evaluate clinical outcomes of dose escalated 3DRT in medically inoperable patients with NSCLC</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definition: NA</p> <p>List of outcomes: OS, CSS</p> <p>Cause of death: Dead: 12 (80%) Dead due to LC: 4 (33%) Dead due to concurrent disease: 8 (67%)</p> <p>Length of FU: NR</p> | <p>Intervention name: 3DRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: Prescribed dose: 92 (N=7 (54%)) or 103 Gy (N=6 (46%)) to PTV 95% isodose line 2.1 Gy fraction daily Once per day, 5 days per week</p> <p>Technical details: Beamenergy NR</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • 1 month after 3DRT, every 3 months for 2 years, every 4 months for the third year, every 6 months for the next 2 years, then annually • Chest Xray every visit, CT scan every 6 months • Toxicity assessed according to SWOG criteria • Patients with disease visualized on bronchoscopy at diagnosis underwent repeat bronchoscopy at 6 months to evaluate local control. • Overall survival (OS) was calculated from the date of the initiation of radiation to the date of death or last follow-up • Deaths due to causes other than lung cancer were censored to determine cause specific survival (CSS) |
| <p>Nyman-2006, #2750</p> | <p>Study Objective: To determine clinical outcomes with SBRT in the treatment of stage I NSCLC in medically inoperable patients</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NA</p> | <p>Intervention name: SBRT</p> <p>Vendor name: CadPlan Treatment Planning System, Varian</p> <p>Dose/frequency/details: Prescribed dose: 45 Gy to the PTV 100% isodose line 3 frs 1 week</p> <p>Technical details:</p> |

| Study | Study Outcomes | Interventions |
|------------------------------|--|---|
| | <p>Definition: NA</p> <p>List of outcomes: OS, CSS, toxicity</p> <p>Cause of death: Dead: 24 (53%) Dead due to LC: 15 (62%) Dead due to concurrent disease: 9 (38%)</p> <p>Length of FU: 43 (24-74) months</p> | <p>6-MeV beam energy</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • 6 weeks, 3 months, 6 months, every 6 months thereafter • Physical exam, performance status, toxicity assessed • CT scan at all time points except 6 weeks • Acute and late toxicity assessed according to EORTC/RTOG scoring system. The acute toxicity was registered during treatment or at the 6-week follow-up visit. • Nine patients who died without tumor progression or metastases were censored at the time of deaths. |
| <p>Olsen-2011, #2792</p> | <p>Study Objective: To compare the efficacy of three lung SBRT regimens in a large institutional cohort</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definition: NA</p> <p>List of outcomes: OS, LCT, toxicity</p> <p>Cause of death: NR</p> <p>Length of FU: Median: 11, 13, 16 months for 3 dose groups</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Pinnacle3 treatment planning system, Philips Medical</p> <p>Dose/frequency/details: Three prescribed dose regimens: Peripheral: 18 Gy X 3 frs = 54 Gy (N=111), Central: 9 Gy X 5 frs = 45 Gy (N=8) OR 10 Gy X 5 frs = 50 Gy (N=11)</p> <p>5 Patients received: 5 frs at incremental doses of 9, 10, 11, and 12 Gy 9 Patients received: 9-10 Gy X 5 frs</p> <p>Technical details: 4D Planning 6-MV photons 8–11 beams</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Duration NR • CT imaging and physician visits • Toxicity scored according to CTCAE v.3.0 |
| <p>Palma 2012, #2843</p> | <p>Study Objective: To evaluate outcomes after SBRT in Patients with severe COPD</p> <p>Primary outcome: NR</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Brainscan v.5.2 treatment planning system, BrainLab, Feldkirchen, Germany</p> |

| Study | Study Outcomes | Interventions |
|-----------------------|--|---|
| | <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of outcomes: OS, LCT, toxicity</p> <p>Cause of death: Total: 62 (35%) Cause NR</p> <p>Length of FU: Median: 21 months</p> | <p>RapidArc linear accelerator, Varian, Palo Alto, CA</p> <p>Dose/frequency/details: Prescribed dose: BrainLab: 3 x 20 Gy, 5 x 12 Gy, or 8 x 7.5 Gy RapdArc: 3 x 18 Gy, 5 x 11 Gy, or 8 x 7.5 Gy</p> <p>80% PTV isodose line</p> <p>Technical details: 6-MV photons 8–12 noncoplanar static beams</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Outpatient assessments at 3-6 month intervals post-SBRT • Diagnostic CT scan at each visit • Toxicity assessed according to CTCAE v.3.0 • Late toxicity defined as >6 weeks after treatment |
| Pennathur-2007, #2896 | <p>Study Objective: To evaluate CT-guided RFA as an alternative treatment option for high-risk medically inoperable patients with stage I NSCLC</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definition: NA</p> <p>List of outcomes: OS, complications</p> <p>Cause of death: Dead: 6 (33%) Dead due to LC: 3 (50%) Dead due to concurrent disease: 2 (33%) Causes of death unknown: 1 (17%)</p> <p>Length of FU:</p> | <p>Intervention name: RFA</p> <p>Vendor name: Generator: RF3000, Boston Scientific, Boston, MA RITA Starburst XL, RITA Medical Systems</p> <p>Needle electrodes: LeVeen, Radiotherapeutics Corporation, Sunnyvale, CA Starburst XL, RITA Medial Systems</p> <p>Dose/frequency/details: RF3000: power 5-10W increments until system impedance > 400 ohm RITA: power 35-50 W, target temperature 90 degrees C</p> <p>Technical details: With both systems, electrode was repositioned as many times as needed to encompass the target tissue and a small rim of about 0.5-1.0 cm nondiseased tissue</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • 3-month intervals |

| Study | Study Outcomes | Interventions |
|-----------------------|--|---|
| | 28 (9-52) months | <ul style="list-style-type: none"> Clinical examination, CT and selective FDG PET scans Modified RECIST criteria were used to assess initial response to treatment at 3 to 5 months The time to progression was calculated from the treatment date. |
| Pennathur-2009, #2898 | <p>Study Objective: To determine the outcomes of SRS in the treatment of stage I NSCLC.</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definition: NA</p> <p>List of outcomes: OS, complications</p> <p>Cause of death: Total: 10 (48%) cause not specified</p> <p>Length of FU: 21 (12-43) months</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Cyberknife, Accuray, Sunnyvale, CA</p> <p>Dose/frequency/details: Hypofractionated Prescribed dose: 20-60 Gy to the 80% PTV isodose line BED: 60-70 Gy 1-3 frs</p> <p>Technical details: 6-MeV beam energy</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> 3-month intervals with CT and FDG PET scans Modified RECIST criteria were used to assess initial response to treatment at 3 months The time to progression was calculated from the treatment date after censoring data from patients who died without progression. |
| Ricardi-2010, #3098 | <p>Study Objective: To evaluate clinical outcomes and toxicity of SBRT in Patients with stage I NSCLC who were medically inoperable or refused surgery</p> <p>Primary outcome: LCT</p> <p>Definition: LCT defined as absence of local failure, diagnosed as tumor growth or re-growth after initial shrinkage</p> <p>Secondary outcome(s): OS, CSS, toxicity</p> <p>Definitions: OS defined as death from any cause after SBRT CSS defined as death due to cancer after SBRT</p> <p>List of outcomes:</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Oncentra OTP 3D treatment planning system, Nucletron, Netherlands Elekta Precise linear accelerator, Elekta, Netherlands</p> <p>Dose/frequency/details: Prescribed dose: (15 Gy x3) 45 Gy to 80% PTV isodose line BED: 124 Gy 3 frs 1 week</p> <p>Technical details: 6–10 MV photons 6–8 noncoplanar static beams Average time for a single session was approximately 45 min</p> <p>Treatment Intention: Curative</p> |

| Study | Study Outcomes | Interventions |
|-------------------------------|---|---|
| | <p>OS, CSS, LCT, toxicity</p> <p>Cause of death: Dead: 20 (32%) Dead due to LC: 12 (60%) Dead due to concurrent disease: 8 (40%)</p> <p>Length of FU: 28 (9-61) months</p> | <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • 6 weeks, then every 3 months after SBRT • Clinical examination and CT scans • Acute and late toxicity assessed according to RTOG criteria • Late toxicity defined as: events occurring after day 90 • Acute toxicity defined as: events occurring between day 1 and day 90 from the start of radiation treatment • RECIST criteria used to evaluate tumor response • Local tumor control was defined as absence of local failure, diagnosed as tumor growth or re-growth after initial shrinkage. <p>Overall survival started from time of SBRT until death from any cause</p> |
| <p>Scorsetti-2007, #3362</p> | <p>Study Objective: To determine clinical outcomes with SBRT in the treatment of stage I NSCLC in medically inoperable patients</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definition: NA</p> <p>List of outcomes: OS, LCT, toxicity</p> <p>Cause of death: Dead: 10 (23%) Dead due to LC: 2 (20%) Dead due to concurrent disease: 8 (80%)</p> <p>Length of FU: 14 (6-36) months</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Ergo TPS treatment planning system</p> <p>Dose/frequency/details: Prescribed dose: 20-32 Gy BED: 40-117 Gy 7-10 Gy per fraction 2-4 frs</p> <p>Technical details: Beam strength NR</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • 45 days, then every 3 months after SBRT • CT scans, spirometry • Toxicity assessed according to RTOG/EORTC criteria • 3 months= acute toxicity after radiotherapy and after 3 months =late toxicity. • Local progression defined as: increase of tumor volume of more than 25% in volume in CT scan and/or increased uptake in PET |
| <p>Shibamoto -2012, #4629</p> | <p>Study Objective: To report a multi-institutional study of SBRT in inoperable and operable patients with histologically confirmed stage I NSCLC</p> <p>Primary outcome: LC at 3-years follow-up</p> <p>Definition: Calculated from the start of SBRT</p> <p>Secondary outcome(s): OS, CSS</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Novalis image-guided system (Varian Medical Systems, Palo Alto, CA) CLINAC 23EX or 21 EXS (Varian)</p> <p>Eclipse v.7.5.14.3 (Varian)</p> |

| Study | Study Outcomes | Interventions |
|---------------------|---|--|
| Song-2009, #3549 | <p>Definitions: Calculated from the start of SBRT</p> <p>List of Outcome(s): OS, CSS, LCT, Toxicity</p> <p>Cause of death: Dead: 65 (36%) NR by operability</p> <p>Length of FU: 36 months NR by operability</p> <p>Study Objective: To evaluate clinical outcomes and toxicity of SBRT as treatment for Patients with primary Stage I NSCLC adjacent to central large bronchus and who are medically inoperable or refuse surgery</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of outcomes: OS, LCT, toxicity</p> <p>Cause of death: NR</p> <p>Length of FU: 26 (5-92) months</p> | <p>BRAINSCAN v.5.31 (BrainLAB, Feldkirchen, Germany) Pinnacle3 (Philips, Madison, WI)</p> <p>Dose/frequency/details: Hypofractionated SBRT Total dose: 44-52 Gy to 90% of the isodose line of PTV in 4 frs for 9-21 days</p> <p>Technical details: 6-MV photons</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> All time intervals were calculated from the start of SBRT CT scans of chest and upper abdomen at 2-months intervals up to 6 months, every 2-4 months thereafter Toxicity: CTCAE v3.0 criteria during and up to 3 months after RT <p>Intervention name: SBRT</p> <p>Vendor name: Render 3-D treatment planning system, Elekta Oncology, Netherlands Eclipse treatment planning system, Varian USA</p> <p>Dose/frequency/details: Prescribed dose: 40-60 Gy to 85% PTV isodose line 3-4 frs 10-20 Gy per fraction 3-4 consecutive days</p> <p>Technical details: 3D Planning Beam energy NR</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> 1, 6, 12 months after SBRT Chest CT Pulmonary toxicity scored by NCI-CTC v. 2.0 Local tumor control was defined as a tumor response of stable disease (SD) or better. Radiation-induced bronchial stricture was initially determined on scheduled follow-up CT scans or simple Chest X-ray by narrowing of bronchus or secondary collapsed lung parenchyma. Some Patients were observed with only follow-up CT scans without additional examination if the radiation-induced stricture was stable. |

| Study | Study Outcomes | Interventions |
|-------------------------|--|---|
| Stephans-2009, #3614 | <p>Study Objective: To assess the impact of fractionation upon tumor control and toxicity in medically inoperable early stage lung cancer patients treated with SBRT</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definition: NA</p> <p>List of outcomes: OS, LCT, toxicity</p> <p>Cause of death: Dead: 25 (29%)</p> <p>Length of FU: 15 (2-48) months</p> | <p>Intervention name: SBRT</p> <p>Vendor name: BrainScan 5.31 treatment planning system, BrainLAB, Feldkirchen, Germany Novalis linear accelerator, BrainLAB</p> <p>Dose/frequency/details: Two fractionation schemes: 60 Gy to 81-90% isodose line 3 frs 8-14 days 50 Gy to 97-100% isodose line 5 frs 5 days</p> <p>Technical details: 6-MeV beam energy</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> 6-8 weeks after SBRT, every 3 months thereafter with CT and pulmonary function test twice annually Toxicity assessed according to CTCAE v.3.0 |
| Taremi-2011, #3732 | <p>Study Objective: To present the results of SBRT for medically inoperable patients with stage I NSCLC and contrast outcomes in patients with and without a pathologic diagnosis</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definition: NA</p> <p>List of outcomes:</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Pinnacle treatment planning system, Philips, Madison, WI Linear accelerator NR</p> <p>Dose/frequency/details: Prescribed dose: 48-60 Gy to the PTV 90% isodose line 3-10 frs Daily fractionation for some regimens, duration NR for all regimens</p> <p>Technical details: Beam energy NR</p> <p>Treatment Intention: Curative</p> |

| Study | Study Outcomes | Interventions |
|-------------------------------|---|--|
| | <p>OS, CSS, LCT, toxicity</p> <p>Cause of death: Dead: 45 (42%) Dead due to LC: 17 (38%) Dead due to concurrent disease: 28 (62%)</p> <p>Length of FU: 19 (1-56) months</p> | <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • 6 weeks after SBRT, then every 3 months for first year, every 6 months in second year, annually thereafter • FDG PET at 3 months after SBRT • CT at 6 and 12 months after SBRT, every 6-12 months thereafter • CTCAE v 3.0 |
| <p>Takeda-2009, #3700</p> | <p>Study Objective: To analyze clinical outcomes of SBRT for patients with stages IA and IB NSCLC</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of outcomes: OS, CSS, LCT, toxicity</p> <p>Cause of death: NR</p> <p>Length of FU: 31 (10-72) mos</p> | <p>Intervention name: SBRT</p> <p>Vendor name: XiO treatment planning system, V.4.2 or v.4.3, CMS, St. Louis, MO</p> <p>Linear accelerator NR</p> <p>Dose/frequency/details: Prescribed dose: 50 Gy to the 80% isodose line 10 Gy per fraction 5 fractions</p> <p>Technical details: Beam energy NR</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Monthly for first 6 mos, with chest X-ray • CT scans at 1 and 3 mos after SBRT, then at 3-mos intervals during first 2 years • FU interviews and CT scans at 4-6 mos intervals after 2 years • Toxicity assessed according to CTCAE v.3.0 |
| <p>Turzer-2011, #3842</p> | <p>Study Objective: To assess SBRT results and toxicity for stage I NSCLC Patients with low performance status and severe comorbidity</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Elekta Synergy linear accelerator, Elekta AB</p> <p>Dose/frequency/details: Prescribed dose: 45 Gy to PTV 100% isodose line 3 frs 1 week</p> <p>Technical details: Beam energy NR</p> <p>Treatment Intention:</p> |

| Study | Study Outcomes | Interventions |
|--|---|---|
| | <p>List of outcomes: OS, LCT, toxicity</p> <p>Cause of death: Dead: 1 (3%)</p> <p>Length of FU: 14 (0-21) months</p> | <p>Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • 6 weeks, 3, 6 months after SBRT. Every 6 months thereafter • Physical examination and chest CT every visit, FDG PET twice annually • Toxicity assessed according to CTCAE v.3.0 criteria |
| <p>Vahdat-2010, #3864</p> | <p>Study Objective: To report serial FGD PET/CT tumor response following Cyberknife radiosurgery for stage IA NSCLC in inoperable patients</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definition: NA</p> <p>List of outcomes: OS, LCT</p> <p>Cause of death: Dead: 3 (15%) Dead due to concurrent disease: 3 (100%)</p> <p>Length of FU: 43 months</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Cyberknife, Accuray</p> <p>Dose/frequency/details: Prescribed dose: 42-60 Gy to PTV 95% isodose line 3 frs</p> <p>Technical details: Beam energy NR</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • FDG PET at 3-6, 9-15, 18-24 months after SBRT |
| <p>van der Voort van Zyp-2009, #3885</p> | <p>Study Objective: To report the clinical outcome of treatment using real-time tumor tracking for 70 Patients with inoperable stage I NSCLC</p> <p>Primary outcome: LCT, OS, CSS</p> <p>Definition: LCT: Calculated from first day of treatment until diagnosis of local recurrence OS: measured from start of SBRT until death from any cause CSS: measured from start of SBRT until death from lung cancer</p> <p>Secondary outcome(s): NR</p> | <p>Intervention name: SBRT</p> <p>Vendor name: On Target treatment planning system, v.3.4.1, Accuray, Sunnyvale, CA Cyberknife Synchrony RTS linear accelerator, Accuray</p> <p>Dose/frequency/details: Prescribed dose: 36-60 Gy to the PTV 70-85% isodose line 3 frs Duration NR</p> <p>Technical details: Beam energy NR</p> <p>Treatment Intention:</p> |

| Study | Study Outcomes | Interventions |
|------------------------|---|---|
| Videtic-2010, #3958 | <p>Definitions: NA</p> <p>List of outcomes: OS, CSS, LCT</p> <p>Cause of death: Dead: 19 (27%) Dead due to LC: 6 (32%) Dead due to concurrent disease: 13: (68%)</p> <p>Length of FU: Median 15 months</p> <p>Study Objective: To validate the use of SBRT using IMRT beams for medically inoperable stage I NSCLC</p> <p>Primary outcome: OS, LCT</p> <p>Definition: Measured from time of diagnosis until death or last patient contact</p> <p>Secondary outcome(s): NR</p> <p>Definition: NA</p> <p>List of outcomes: OS, LCT, toxicity</p> <p>Cause of death: Dead: 14 (54%) Dead due to LC: 8 (57%) Dead due to concurrent disease: 6 (43%)</p> <p>Length of FU: 31 (10-51) months</p> | <p>Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Clinical examination and chest CT 3 weeks, 2-3, 6, 9, 12, 18, 24, 30 months thereafter • Toxicity assessed according to CTCAE v.3.0 criteria • Toxicity was acute if it occurred within 4 months and late if it occurred thereafter <p>Intervention name: SBRT with IMRT beams</p> <p>Vendor name: Novalis-BrainLAB treatment system</p> <p>Dose/frequency/details: Prescribed dose: 50 Gy to the 95% isodose line 5 frs 5 days</p> <p>Technical details: Beam energy NR</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Initially 6-8 weeks after SBRT, every 3 months for 2 years thereafter • Chest CT scan at each visit with same-day pulmonary function test twice annually • Toxicity assessed according to CTCAE v.3.0 criteria |

Appendix Table C3. Survival and local control outcomes of studies that address Key Question 1

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|------------------------|---|--|--|--|------------|
| Andratschke 2011, #132 | SBRT: Overall survival: Median 29 months 1-year: 79% 3-years: 38% 5-years: 17% Cancer/disease specific survival: Median 46 months 1-year: 93% 3-years: 64% 5-years: 48% | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 1-year: 89% 3-years: 83% 5-years: 83% | Local control: NA | No |
| Baumann 2006, #271 | SBRT Overall survival: 3-year: 52% 5-year: 26% Cancer/disease specific survival: 3-year: 66% 5-year: 40% | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 88% Time to failure: 17.8 (10-49) months | Local control: NA | No |
| Baumann 2009, #270 | SBRT Overall survival: Median: 40.6 months 1-year: 68% 2-years: 65% 3-years: 60% Cancer/disease specific survival: 1-year: 93% 2-years: 88% 3-years: 88% | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 3-years: 92% | Local control: NA | No |
| Bogart-2010, #382 | 3DRT Overall survival: Median: 38.5 months (95% CI: 22.4 to 58.7) Cancer/disease specific survival: NR | Overall survival: NA Cancer/disease specific survival: NA | 3DRT Local control: 93% | Local control: NA | No |
| Bollineni-2012, #4548 | SBRT: Overall survival: | Overall survival: NA | SBRT Local control: | Local control: NA | No |

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|--------------------|--|--|--|---|-----|
| | Median NR 2-years high SUV: 62% 2-years low SUV: 81% | | 2-years: 96% | | |
| | Cancer/disease specific survival: Median NR 2-years high SUV: 74% 2-years low SUV: 90% | Cancer/disease specific survival: NA | | | |
| Bradley-2003, #445 | 3DRT Overall survival: 1-year: 73% 2-year: 51% 3-year: 34% | Overall survival: NA Cancer/disease specific survival: NA | 3DRT Local control: 1-year: 88% 2-year: 69% 3-year: 63% | Local control: NA | No |
| | Cancer/disease specific survival: 1-year: 82% 2-year: 67% 3-year: 51% | | | | |
| Burdick-2010, #521 | SBRT Overall survival: 2-year: 33% (95% CI: 18%-51%) Cancer/disease specific survival: NR | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 2-year: 94% | Local control: NA | No |
| Bush-2004, #535 | PBRT Overall survival: Total 3-year: 44% Rx 51 CGE, 3-year: 27% Rx: 60 CGE, 3-year: 55% (p=0.03) | Overall survival: NA Cancer/disease specific survival: NA | PBRT Local control: 3-year:74% | Local control: NA | No |
| | Cancer/disease specific survival: 3-year: 72% | | | | |
| Campeau 2009, #565 | 3DRT Overall survival: 2-year: 61.3% | Overall survival: NA Cancer/disease specific survival: NA | 3DRT Local control: 2-year: 85% | Local control: NA | No |
| | Cancer/disease specific survival: NR | | | | |
| Coon-2008, #803 | SBRT Overall survival: | Overall survival: NA | SBRT Local control: | Local control: NA | No |

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|---------------------|--|--|---|---|-----|
| | 11 months: 81% | | 11 months: 85% | | |
| | Cancer/disease specific survival: NR | Cancer/disease specific survival: NA | | | |
| Dunlap-2010, #1032 | SBRT Overall survival: Median: 20.1 months (95% CI: 18.7-28.4) 1-year: 85% 2-year:45% | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 2-year: 83% Stage IA, 2-years:90% Stage IB, 2-years: 70% (p=0.035) | Local control: NA | No |
| Fritz-2008, #1238 | SBRT Overall survival: Median:37 months 2-year: 66% 3-year:53% | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 3-year: 81% | Local control: NA | No |
| Graham-2006, #1403 | 3DRT Overall survival: Median 43 months 5-years: 30% (95% CI: 13-48%) | Overall survival: NA Cancer/disease specific survival: NA | 3DRT Local control: NA | Local control: NA | No |
| Iwata-2010, # 1747 | Overall survival: 3-years: 65% | Overall survival: NA | Local control: NR | Local control: NA | Yes |
| | Cancer/disease specific survival: NR | Cancer/disease specific survival: NA | | | |
| Jimenez-2010, #1842 | 3DRT Overall survival: 3-years: 44% (95% CI: 28-58%) | Overall survival: NA Cancer/disease specific survival: NA | 3DRT Local control: NR | Local control: NA | No |
| | Cancer/disease specific survival: NR | | | | |

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|----------------------|--|--|---|--|------------|
| Kopek-2009, #2040 | SBRT Overall survival: Median 22 months 1-year: 67% 2-years: 49% 3-years: 36% 4-years: 24% 5-years: 21% Cancer/disease specific survival: Median 61 months | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 4-years: 89% | Local control: NA | No |
| Mirri-2009, #2576 | 3DRT Overall survival: 1-year: 81% 3-years: 61% Cancer/disease specific survival: NR | Overall survival: NA Cancer/disease specific survival: NA | 3DRT Local control: 1-year: 88% 3-years: 72% | Local control: NA | No |
| Nakayama 2010, #2684 | PBRT Overall survival: 2-years: 98% (95% CI, 94-102%) Cancer/disease specific survival: 2-years: 100% | Overall survival: NA Cancer/disease specific survival: NA | PBRT Local control: 2-years: 97% (95% CI, 91-103%) | Local control: NA | No |
| Narayan-2004, #2686 | 3DRT Overall survival: 2-years: 54% 3-years: 33% Cancer/disease specific survival: 2-years: 76% 3-years: 48% | Overall survival: NA Cancer/disease specific survival: NA | 3DRT Local control: 77% | Local control: NA | No |
| Nyman-2006, #2750 | SBRT Overall survival: Median: 39 months 1-year: 80% 2-years: 71% 3-years: 55% 5-years: 30% Cancer/disease specific survival: Median: 55 months 1-year: 88% | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 80% | Local control: NA | No |

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|-----------------------|---|--|--|---|-----|
| | 2-years: 83% 3-years: 67% 5-years: 41% | | | | |
| Olsen-2011, #2792 | SBRT Overall survival: Median overall : 14 months (not reached) Median 34 months for each dose group Cancer/disease specific survival: NR | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 45 Gy: 1-year: 75% 2-years: 50% 50 Gy: 1-year: 100% 2-years: 100% 54 Gy: 1-year: 99% 2-years: 91% | Local control: NA | No |
| Palma 2012, #2843 | SBRT Overall survival: Median: 32 months 1-year: 79% 3-years: 47% 5-years: 28% Cancer/disease specific survival: NR | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 3-years: 89% | Local control: NA | No |
| Pennathur 2007, #2896 | RFA Overall survival: Median not reached Probability at 1-year: 95% (95% CI, 85-100%) Probability at 2-years: 68% (95% CI, 49-96%) Cancer/disease specific survival: NR | Overall survival: NA Cancer/disease specific survival: NA | RFA Local control: 58% | Local control: NA | |
| Pennathur 2009, #2898 | SBRT Overall survival: Median 26.4 (68% CI, 19.6-not reached) months 1-year: 81% (68% CI, 73-90%) Cancer/disease specific survival: NR | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 58% | Local control: NA | No |
| Ricardi-2010, #3098 | SBRT Overall survival: Median not reached | Overall survival: NA | SBRT Local control: 3-years: 88% | Local control: NA | No |

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|------------------------------|---|--|---|---|-----|
| | 2-years: 69% 3-years: 57% Cancer/disease specific survival: 2-years: 79% 3-years: 72% | Cancer/disease specific survival: NA | | | |
| Scorsetti-2007, Italy, #3362 | SBRT Overall survival: 1-year: 93±5% 2-years: 53±11% Cancer/disease specific survival: NR | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: NR | Local control: NA | No |
| Shibamoto 2012, #4629 | SBRT: Overall survival: Median ~52 months 3-years: 59% 5-years: 44% Cancer/disease specific survival: NR by operability | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: NR by operability | Local control: NA | No |
| Song-2009, #3549 | SBRT Overall survival: 1-year: 71% 2-years: 38% Cancer/disease specific survival: NR | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 1-year: 85% 2-years: 85% | Local control: NA | No |
| Stephans 2009, #3614 | SBRT Overall survival: 1-year: 81% (all patients) 1.5-years: 75% (all patients) 1-year: 83% (50 Gy) 1-year: 77% (60 Gy) Cancer/disease specific survival: NR | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 6-months:100% (all patients) 1-year: 98% (all patients) 1.5-years: 95% (all patients) 1-year: 97% (50 Gy) 1-year: 100% (60 Gy) | Local control: NA | No |
| Taremi-2011, Canada, #3732 | SBRT Overall survival: | Overall survival: NA | SBRT Local control: | Local control: NA | No |

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|-----------------------------------|---|--|---|---|-----|
| | All patients 1-year: 84% (95% CI, 76-90%) 4-years: 30% (95% CI, 15-46%) Cancer/disease specific survival: NA Cancer/disease specific survival: All patients 1-year: 92% (95% CI, 87-98%) 4-years: 77% (95% CI, 64-89%) | Cancer/disease specific survival: NA | All patients 1-year: 92% (95% CI, 86-97%) 4-years: 89% (95% CI, 81-96%) Biopsy-proven 1-year: 93% (95% CI, 87-98%) Nonbiopsy-proven 1-year: 87% (95% CI, 76-99%) p = 0.41 versus biopsy-proven | | |
| Takeda-2009, #3700 | SBRT Overall survival: 3-years: 90% (stage IA) 3-years: 63% (stage IB) p = 0.09 3-years: 77% (inoperable) p = 0.31 Cancer/disease specific survival: 3-years: 100% (stage IA) 3-years: 81% (stage IB) p = 0.10 3-years: 94% (inoperable) p = 0.66 | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 3-years: 93% (stage IA) 3-years: 96% (stage IB) p = 0.86 | Local control: NA | No |
| Turzer-2011, #3842 | SBRT Overall survival: 97% (calculated) Cancer/disease specific survival: NR | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 1.5 years: 100% | Local control: NA | No |
| Vahdat-2010, #3864 | SBRT Overall survival: 2-years: 90% Cancer/disease specific survival: 85% (calculated) | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 2-years: 95% | Local control: NA | No |
| van der Voort van Zyp-2009, #3885 | SBRT Overall survival: 1-year: 83% (95% CI, 71-90%) 2-years: 62% (95% CI, 45-75%) Cancer/disease specific survival: 1-year: 94% 2-years: 86% | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 60 Gy 2-years: 78% (95% CI, 84-99%) 45 Gy 2-years: 78% (95% CI, 37-94%) | Local control: NA | No |

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|---------------------|--|--|--|--|------------|
| Videtic-2010, #3958 | SBRT Overall survival: Median 38 months 3-years: 52% Cancer/disease specific survival: SBRT 69% (calculated) | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 3-years: 94% | Local control: NA | No |

Appendix Table C4. Miscellaneous outcomes of studies that address Key Question 1

| Study | Intervention Group 1 | Intervention Group 2 |
|------------------------|--|---|
| Andratschke-2011, #132 | <p>SBRT: Lung function: NR</p> <p>Obstructive symptoms: NR</p> <p>Quality of life: NR</p> <p>Performance status: NR</p> <p>Others: NR</p> | <p>Lung function: NA</p> <p>Obstructive symptoms: NA</p> <p>Quality of life: NA</p> <p>Performance status: NA</p> <p>Others: NA</p> |
| Baumann 2008, #270 | <p>SBRT Lung function: Baseline FEV1%: 49.0 (20.0-162.0) Post Rx FEV1% (at 14.3 months [3.0-33.4]): 52.5 (19.0-167.0)</p> <p>Obstructive symptoms: NR</p> <p>Quality of life: NR</p> <p>Performance status: NR</p> <p>Others: NA</p> | <p>Lung function: NA</p> <p>Obstructive symptoms: NA</p> <p>Quality of life: NA</p> <p>Performance status: NA</p> <p>Others: NA</p> |
| Baumann-2006, #271 | <p>SBRT Lung function: NR</p> <p>Obstructive symptoms: NR</p> <p>Quality of life: NR</p> <p>Performance status: NR</p> <p>Others: NA</p> | <p>Lung function: NA</p> <p>Obstructive symptoms: NA</p> <p>Quality of life: NA</p> <p>Performance status: NA</p> <p>Others: NA</p> |

| Study | Intervention Group 1 | Intervention Group 2 |
|--------------------------|---|--|
| Bogart-2010, #382 | 3DRT Lung function: A significant trend for changes in pulmonary function was not observed. Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Bollineni-2012, #4548 | SBRT: Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Bradley-2003, #445 | 3DRT Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Burdick-2010, #521 | SBRT Lung function: NR | Lung function: NA Obstructive symptoms: |

| Study | Intervention Group 1 | Intervention Group 2 |
|-----------------------|-------------------------------------|------------------------------------|
| | Obstructive symptoms: NR | NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: NA | Others: NA |
| Bush-2004, #535 | PBRT Lung function: NR | Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: NA | Others: NA |
| Campeau-2009, #565 | 3DRT Lung function: NR | Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: NA | Others: NA |

| Study | Intervention Group 1 | Intervention Group 2 |
|-----------------------|---|--|
| Coon-2008, #803 | SBRT Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NA | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Dunlap-2010, #1032 | SBRT Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NA | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Fritz-2008, #1238 | SBRT Lung function: Pre:0.66-2.93 Post (1-year):0.6-2.5 Post (2-years):0.8-2.1 Post (3-years): 1.1-1.9 Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NA | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Graham-2006, | 3DRT | 3DRT |

| Study | Intervention Group 1 | Intervention Group 2 |
|---------------------|--|--|
| #1403 | Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Iwata-2010, #1747 | PBRT Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | PBRT Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Jimenez-2010, #1842 | 3DRT Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | 3DRT Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Kopek-2009, #2040 | SBRT Lung function: NR Obstructive symptoms: | SBRT Lung function: NA Obstructive symptoms: |

| Study | Intervention Group 1 | Intervention Group 2 |
|-------------------------|--|-------------------------------------|
| | NR | NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: ≥ 3 performance status decline from baseline: 4 (5%) | Performance status: NA |
| | Others: NR | Others: NA |
| Mirri-2009, #2576 | 3DRT Lung function: NR | 3DRT Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: NR | Others: NA |
| Nakayama 2010, #2684 | PBT Lung function: Fletcher-Hugh-Jones criteria: Decline: 2 (4%) | PBT Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: NR | Others: NA |
| Narayan-2004, #2686 | 3DRT Lung function: NR | 3DRT Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: | Quality of life: |

| Study | Intervention Group 1 | Intervention Group 2 |
|----------------------|-------------------------------------|-------------------------------------|
| | NR | NA |
| | Performance status: NR | Performance status: NA |
| | Others: NR | Others: NA |
| Nyman-2006, #2750 | SBRT Lung function: NR | SBRT Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: NR | Others: NA |
| Olsen-2011, #2792 | SBRT Lung function: NR | SBRT Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: NR | Others: NA |
| Palma 2012, #2843 | SBRT Lung function: NR | SBRT Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |

| Study | Intervention Group 1 | Intervention Group 2 |
|-----------------------|-------------------------------------|-------------------------------------|
| | Others: NR | Others: NA |
| Pennathur-2007, #2896 | RFA Lung function: NR | RFA Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: NR | Others: NA |
| Pennathur-2009, #2898 | SBRT Lung function: NR | SBRT Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: NR | Others: NA |
| Ricardi-2010, #3098 | SBRT Lung function: NR | SBRT Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: NR | Others: NA |
| Scorsetti-2007, | SBRT | SBRT |

| Study | Intervention Group 1 | Intervention Group 2 |
|-----------------------|---|--|
| #3362 | Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Shibamoto-2012, #4629 | SBRT: Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Song-2009, #3549 | SBRT Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | SBRT Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Stephans-2009, #3614 | SBRT Lung function: NR Obstructive symptoms: | SBRT Lung function: NA Obstructive symptoms: |

| Study | Intervention Group 1 | Intervention Group 2 |
|-----------------------|--|--|
| | NR Quality of life: NR Performance status: NR Others: NR | NA Quality of life: NA Performance status: NA Others: NA |
| Taremi-2011, #3732 | SBRT Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | SBRT Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Takeda-2009, #3700 | SBRT Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | SBRT Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Turzer-2011, #3842 | SBRT Lung function: NR Obstructive symptoms: NR Quality of life: NR | SBRT Lung function: NA Obstructive symptoms: NA Quality of life: NA |

| Study | Intervention Group 1 | Intervention Group 2 |
|---|--|-------------------------------------|
| | Performance status: NR | Performance status: NA |
| | Others: NR | Others: NA |
| Vahdat-2010, #3864 | SBRT Lung function: NR | SBRT Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: NR | Others: NA |
| van der Voort van Zyp-2009, #3885 | SBRT Lung function: NR | SBRT Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: NR | Others: NA |
| Videtic-2010, #3958 | SBRT Lung function: Median post-treatment FEV1: 1.17 (range NR) | SBRT Lung function: NA |
| | Obstructive symptoms: NR | Obstructive symptoms: NA |
| | Quality of life: NR | Quality of life: NA |
| | Performance status: NR | Performance status: NA |
| | Others: | Others: |

| Study | Intervention Group 1 | Intervention Group 2 |
|-------|----------------------|----------------------|
| | NR | NA |

Appendix Table C5. Toxicity outcomes of studies that address Key Question 1

| Study | Intervention Group 1 | Intervention Group 2 |
|---------------------------|---|-----------------------------|
| Andratschke 2011, #132 | SBRT: Hemoptysis: 2 (2%) Grade 2 pneumonitis: 12 (13%) Grade 3 pneumonitis: 2 (2%). Grade 3 dyspnea: 7 (8%) Grade 4 dyspnea: 4 (4%) Grade 2 thoracic wall pain: 4 (4%) Grade 3 fatigue (late): 1 (1%) Rib fractures: 3 (3%) Benign pleural effusion: 4 (4%) Atelectasis: 2 (2%) | NA |

| Study | Intervention Group 1 | Intervention Group 2 |
|------------------------------|---|----------------------|
| Baumann-2006, #271 | SBRT Toxicities Total: 83 (60%) Grade 3-4: Thoracic pain: 4 (3%) Lung atelectasis: 2 (1%) Rib fracture: 2 (1%) Decreased Lung function: 2 (1%) Decreased Performance status: 2(1%) Pneumonitis: 1 (0.7%) Pneumonia: 1 (0.7%) < Grade 3: Lung Fibrosis: 21 (15%) Skin rash: 12 (9%) Lung atelectasis: 8 (6%) Esophagitis: 5 (4%) Pleural exudates: 4 (3%) Thoracic Pain: 2 (1%) Nausea: 1(0.7%) | NA |
| Baumann-2009, #270 | SBRT Grade 3 (≤18 months): Dyspnea: 4 (7%) Cough: 1 (2%) Pneumonia: 1 (2%) Fibrosis: 2 (4%) Atelectasis: 1 (2%) Pleural effusion: 2 (4%) Heart disorder: 1 (2%) Rib fracture: 1 (2%) Pain: 2(4%) Fatigue: 1 (2%) Grade 3 (>18 months): Rib fracture: 1 (2%) Heart failure: 1 (2%) Fibrosis: 1 (2%) Grade 4 at 36 months: Dyspnea: 1(2%) | NA |
| Bogart-2010, #382 | 3DRT Grade 3 hematological toxicity: 1 (3%) Grade 3 dyspnea: 1 (3%) Grade 3 pain: 1 (3%) | NA |
| Bollineni-2012, #4548 | SBRT NR | NA |
| Bradley-2003, #445 | 3DRT Grade 3-4 Esophagitis: 2 (4%) Grade 3 Pneumonitis: 1 (2%) Grade 4 Pneumonitis: 1 (2%) Acute: Grade 1-2: Esophagitis: 14 (25%) | NA |

| Study | Intervention Group 1 | Intervention Group 2 |
|------------------------|--|----------------------|
| | Grade 1-2: Pneumonitis: 3 (5%) Late: Grade 1-2: Esophagitis: 2 (4%) Grade 1-2: Pneumonitis: 19 (34%) | |
| Burdick-2010, #521 | SBRT NR | NA |
| Bush-2004, #535 | PBRT Acute toxicities were limited to mild fatigue and radiation dermatitis that was seen as mild-to-moderate erythema. These required no specific medical treatment. No cases of clinical acute radiation pneumonitis were identified. No patient required steroids or anti-inflammatory therapy. No cases of acute or late esophageal or cardiac toxicity were identified. | NA |
| Campeau-2009, #565 | 3DRT 3 patients did not complete treatment due to treatment related toxicities. Details of toxicities not reported | NA |
| Coon-2008, #803 | SBRT Grade 2: Pneumonitis: 1 (1 %) | NA |
| Dunlap-2010, #1032 | SBRT Grade 2: Pneumonitis: 1 (3%) Grade 3: Pneumonitis: 1 (3%) Rib fracture: 2 (5%) Chest wall pain: 9 (23%) | NA |
| Fritz-2008, #1238 | SBRT Grade 4: rib fracture: 2 (5%) | NA |
| Graham-2006, #1403 | 3DRT Grade 2 pneumonitis: 3 (8%) | NA |
| Iwata-2010, # 1747 | PBRT 60 Gy: RP Grade 2: 4 (10.8%) RP Grade 3: 0 Dermatitis Grade 2: 4 (10.8%) Dermatitis Grade 3: 0 Rib fracture Grade 2: 6 (16.2%) Soft Tissue Grade 2: 2 (5.4%) PBRT 80Gy: To be extracted RP Grade 2: 3 (15.0%) RP Grade 3: 1 (5.0%) Dermatitis Grade 2: 4 (20.0%) Dermatitis Grade 3: 3 (15.0%) Rib fracture Grade 2: 9 (45.0) Soft Tissue Grade 2: 2 (10.0%) | NA |
| Jimenez-2010, #1842 | 3DRT NR | NA |
| Kopek-2009, | SBRT | NA |

| Study | Intervention Group 1 | Intervention Group 2 |
|----------------------|--|----------------------|
| #2040 | Grade 2: Esophagitis: 1 (1%) Pain: 9 (10%) Analgesia: 5 (6%) Dyspnea: 9 (10%) Pulmonary fibrosis: 2 (2%) Pneumonitis: 1 (1%) Pleural effusion: 2 (2%) Skin hyperpigmentation: 2 (2%) Skin erythema: 1 (1%) ≥ 3 grade point worsening in analgesia use from baseline: 7 (8%) Grade ≥3: Dyspnea: 11 (%) Analgesia: 9 (10%) Pain: 2 (2%) Cough: 1 (1%) Rib fracture: 7 (8%) | |
| Mirri-2009, #2576 | 3DRT Late Grade 2 pulmonary: 2 (13%) *One patient, affected by dilated cardiomyopathy, developed pericardial effusion 3 months after the end of radiotherapy. However, because of the previous cardiac problems, it was difficult to assess whether this was radiation related. | NA |
| Nakayama 2010, #2684 | PBT Grade 2 pneumonitis: 2 (4%) Grade 3 pneumonitis: 2 (4%) Grade 3 pulmonary dysfunction: 1 (2%) Rib fracture: 1 (2%) | NA |
| Narayan-2004, #2686 | 3DRT Grade 2 esophagitis: 1 (9%) No patient developed Grade 2 or higher pneumonitis | NA |
| Nyman-2006, #2750 | SBRT 23 (51%) did not experience any acute toxicity. No Grade 2 or greater pneumonitis reported Late: Rib fractures: 2 (4%) Atelectasis: 3 (7%) | NA |
| Olsen-2011, #2792 | SBRT Chest wall pain requiring analgesia: 21 (16%) Grade 2 radiation pneumonitis: 4 (3%) No Grade 3 or greater toxicities reported | NA |
| Palma 2012, #2843 | SBRT Acute Grade 3 pneumonitis: 1 (< 1%) Late Grade 3 pneumonitis: 2 (1%) | NA |

| Study | Intervention Group 1 | Intervention Group 2 |
|-----------------------------------|--|----------------------|
| | Late Grade 3 hemoptysis: 1 (< 1%) Rib fractures: 2 (1%) | |
| Pennathur-2007, #2896 | RFA Pneumothorax: 12 (63%) Prolonged air leak (> 5 days): 1 (5%) No procedure-related deaths | NA |
| Pennathur-2009, #2898 | SBRT No radiation-associated adverse effects were reported Pneumothorax secondary to fiducial placement: 10 (47%) No procedure-related deaths | NA |
| Ricardi-2010, #3098 | SBRT Late Grade 3 radiation pneumonitis: 2 (3%) Rib fracture: 1 (2%) | NA |
| Scorsetti-2007, #3362 | SBRT Acute Grade 2 pneumonitis: 2 (5%) Late Grade 2 pneumonitis: 1 (2%) | NA |
| Shibamoto -2012, #4269 | SBRT: NR by operability | NA |
| Song-2009, #3549 | SBRT Grade 3 pneumonitis: 3 (9%) Partial or complete bronchial stricture: 8 (25%) Grade 5 hemoptysis: 1 (3%) No severe skin, esophageal or rib fractures were reported | NA |
| Stephans-2009, #3614 | SBRT Grade 2 pneumonitis: 2 (2%) Grade 1 or 2 chest wall toxicity: 9 (10%) | NA |
| Taremi-2011, #3732 | SBRT Acute Grade 3 fatigue: 1 (1%) Acute Grade 3 dyspnea: 2 (2%) Acute Grade 3 chest wall pain: 1 (1%) Late Grade 3 rib fracture: 3 (3%) Late Grade 3 dyspnea: 2 (2%) Late Grade 3 pneumonia: 1 (1%) No Grade 4 or 5 toxicities were observed | NA |
| Takeda-2009, #3700 | SBRT No acute toxicity was observed Grade 2 pneumonitis: 1 (2%) Grade 3 pneumonitis: 2 (3%) Grade 5 bacterial pneumonia at site of Grade 3 radiation pneumonitis: 1 (2%) | SBRT NA |
| Turzer-2011, #3842 | SBRT Grade 2 pneumonitis: 1 (3%) Grade 3 pneumonitis: 1 (3%) | NA |
| Vahdat-2010, #3864 | SBRT NR | NA |
| van der Voort van Zyp 2009, #3885 | SBRT Grade 3 pneumothorax: 1 (1%) Grade 3 cardiac arrhythmia: 1 (1%) | NA |

| Study | Intervention Group 1 | Intervention Group 2 |
|------------------------|---|----------------------|
| Videtic-2010, #3958 | Acute Grade 3 thoracic pain: 1 (1%) Late Grade 3 pneumonitis: 3 (4%) Late Grade 3 thoracic pain: 4 (6%) No Grade 4 or 5 toxicities were observed | NA |
| | SBRT Acute Grade 3 dyspnea: 1 (4%) Late Grade 2 chest wall pain: 1 (4%) No Grade 4 or 5 toxicities were observed | |

Appendix Table C6. Attributes of studies that address Key Question 1

| ID | HC | Enroll Start | Enroll End | Design | Study Setting | Treatment Setting | Institution Setting(s) | Stage(s) | Staging Criteria | COI | Funding |
|-------------------------|---------|--------------|------------|--------|---------------|-------------------|------------------------|----------|---------------------------------------|-----|---------|
| Andratschke, 2011, #132 | Y | 12/00 | 03/10 | RET | SI | NR | TH | I | AJCC 2002 | N | G |
| Baumann, 2006, #271 | N (24%) | XX/96 | XX/03 | RET | M | NR | NR | I | NR | NR | NR |
| Baumann, 2009, #270 | N (33%) | 08/03 | 09/05 | PRO | M | NR | NR | I | NR | NR | OH |
| Bogart, 2009, #382 | Y | 12/00 | 07/05 | PRO | NR | NR | NR | I | NR | Y | MA |
| Bollineni-2012, #4548 | N (70%) | 11/06 | 02/10 | RET | SI | NR | TH | I | AJCC 2002 | N | NR |
| Bradley, 2003, #445 | Y | XX/91 | XX/01 | PRO | NR | NR | NR | I | AJCC 2002 | NR | NR |
| Burdick, 2010, #521 | N (32%) | 10/03 | 08/07 | RET | SI | NR | TH | I | AJCC 2002 | N | NR |
| Bush, 2004, #535 | Yes | NR | NR | PRO | SI | NR | TH | I | NR | NR | S |
| Campeau, 2009, #565 | Yes | 01/00 | 12/05 | RET | SI | NR | NR | I | Union Internationale Contre le Cancer | NR | NR |
| Coon, 2008, #803 | N (39%) | 01/05 | 01/07 | RET | SI | NR | TH | I | AJCC 2002 | NR | NR |
| Dunlap, 2010, #1032 | Yes | 03/05 | 01/08 | RET | SI | NR | TH | I | AJCC 2002 | NR | NR |
| Fritz, 2008, #1238 | Yes | NR | NR | RET | SI | NR | NR | I | NR | N | NR |
| Graham, 2006, #1403 | Yes | 01/95 | 12/02 | RET | M | NR | TH | I | NR | NR | NR |
| Iwata, 2010, #1747 | Yes | 04/03 | 04/07 | PRO | SI | NR | TH | I | IUAC 2002 | N | G |
| Jimenez, 2010, #1842 | Yes | 09/05 | 04/07 | RET | SI | NR | TH | I | NR | N | NR |
| Kopek, 2009, #2040 | Yes | 01/00 | 12/07 | PRO | SI | NR | TH | I | IUAC 1997 | NR | MA,S,G |
| Mirri, 2009, #2576 | N (27%) | 06/03 | 03/07 | PRO | SI | NR | TH | I | NR | NR | NR |
| Nakayama, 2010, #2684 | N (12%) | 11/01 | 07/08 | RET | M | NR | TH | I | IUAC2002 | NR | NR |

| ID | HC | Enroll Start | Enroll End | Design | Study Setting | Treatment Setting | Institution Setting(s) | Stage(s) | Staging Criteria | COI | Funding |
|------------------------------------|---------|--------------|------------|--------|---------------|-------------------|------------------------|----------|------------------|-----|---------|
| Narayan, 2004, #2686 | Yes | NR | NR | PRO | M | NR | TH | I | NR | NR | G |
| Nyman, 2006, #2750 | N (20%) | 09/98 | 03/03 | RET | SI | NR | TH | I | NR | NR | NR |
| Olsen, 2011, #2792 | N (15%) | 06/04 | 06/09 | PRO | SI | NR | TH | I | AJCC 2009 | N | NR |
| Palma, 2011, #2843 | N (68%) | 01/03 | 03/10 | PRO | SI | NR | TH | I | NR | Y | NR |
| Pennathur, 2007, #2896 | Yes | 01/02 | 12/05 | RET | SI | NR | TH | I | NR | Y | MA,G |
| Pennathur, 2009, #2898 | N (5%) | 01/02 | 12/05 | RET | SI | NR | TH | I | NR | NR | NR |
| Ricardi, 2010, #3098 | N (36%) | 05/03 | 08/07 | PRO | SI | NR | TH | I | NR | N | NR |
| Scorsetti, 2007, #3362 | N (5%) | 01/04 | 01/06 | NR | M | NR | TH | I | NR | NR | NR |
| Shibamoto, 2012, #4269 | Y | 05/04 | 11/08 | PRO | M | NR | TH | I | IUAC2002 | N | NR |
| Song, 2009, #3549 | Yes | 06/99 | 05/06 | RET | SI | NR | TH | I | AJCC 2002 | N | G |
| Stephans, 2009, #3614 | N (29%) | 02/04 | 08/07 | RET | SI | NR | TH | I | AJCC 2002 | N | NR |
| Taremi, 2012, #3732 | N (25%) | 12/04 | 10/08 | PRO | SI | NR | TH | I | NR | N | MA,S,G |
| Takeda-2009, #3700 | N(18%) | 12/01 | 05/07 | RET | M | NR | TH | I | NR | N | NR |
| Turzer, 2011, #3842 | N (26%) | 09/08 | 04/10 | RET | SI | NR | TH | I | NR | NR | NR |
| Vahdat, 2010, #3864 | Yes | 01/05 | 01/08 | PRO | SI | NR | TH | I | NR | Y | NR |
| van der Voort van Zyp, 2009, #3885 | N (49%) | 08/05 | 10/07 | NR | SI | NR | TH | I | NR | N | NR |
| Videtic, 2010, #3958 | N (29%) | 10/03 | 11/06 | RET | SI | NR | TH | I | AJCC 2002 | N | NR |

Appendix Table C7. Description of studies that address Key Question 2

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient characteristics |
|---------------------------|--|---|---|---|---|
| Chen-2012, USA, #4554 | <p>Study design: PRO, SAS</p> <p>Patients enrolled: 40 (100%)</p> <p>Lost to FU/excluded/missing: 0</p> | <p>Inclusion criteria: 1. Hst confirmed, primary clinical stage I NSCLC</p> <p>2. Medically operable, high risk</p> <p>Exclusion criteria: Inability to safely implant fiducials for tumor tracking</p> | <p>Stage I: 40 (100%)</p> | <p>Location: NR</p> <p>Histopathology: Hst confirmed: 40 (100%) ACC: 19 (48%) SCC: 12 (30%) NSCLC NOS: 9 (22%)</p> | <p>Age (years): Median 76 (63-87)</p> <p>Women: 24 (60%)</p> <p>Race: Caucasian 33 (82%)</p> <p>Co-morbidities: Mean DLCO 10 (3.5-23.3 mL/min/mm Hg) Predicted mean DLCO 55% (14-128%) Predicted mean FEV1 57% (21-111%)</p> <p>Current or former smoker: 38 (95%)</p> <p>Performance status: Median ECOG 1 (0-2)</p> |
| Iwata-2010, Japan, # 1747 | <p>Study design: NRCS, NR whether data collection was RET or PRO</p> <p>Patients enrolled: Total: 57 (100%) PBRT 80Gy: 20 (35%) PBRT 60 Gy: 37 (65%)</p> <p>Refusal: Total: 28 (100%) PBRT 80Gy: 10 (34%) PBRT 60 Gy: 18 (64%)</p> <p>Lost to FU/excluded/missing: None</p> | <p>Inclusion criteria:</p> <p>1. Hst confirmed primary NSCLC staged IA or IB (International Union Against Cancer 2002 staging system)</p> <p>2. Medically inoperable or refused surgical resection</p> | <p>Total: 57 (100%) Stage 1A: 27(47%) Stage 1B: 30 (57%)</p> <p>PBRT 80Gy: 20 (100%) Stage 1A: 6 (30%) Stage 1B: 14(70%)</p> <p>PBRT 60 Gy: 37 (100%) Stage 1A: 21 (57%) Stage 1B: 16 (43%)</p> | <p>Location: NR</p> <p>Histopathology: Total: 57 (100%) AC: 32 (56%) SCC: 23 (40%) Others: 2 (4%)</p> <p>PBRT 80Gy: 20 (100%) AC: 11 (55%) SCC: 8 (40%) Others: 1 (5%)</p> <p>PBRT 60 Gy: 37 (100%) AC: 21 (57%) SCC: 15 (41%) Others: 1 (3%)</p> | <p>Age: Total: 76 (48-89) PBRT 80Gy: 75 (48-87) PBRT 60 Gy: 78 (57-87)</p> <p>Women: Total: 23 (29%) PBRT 80Gy: 7 (36%) PBRT 60 Gy: 7 (19%)</p> <p>Race: NR</p> <p>Co-morbidities: Total: 28 (100%) Pulmonary: 13 (46%) CVD: 9 (32%) Severe DM: 5 (18%) Age: 2 (7%) Others: 2 (7%)</p> |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient characteristics |
|---|---|--|----------------------------|--|---|
| | | 3. WHO performance status ≤ 2 4. No history of previous LC 5. No prior chest RT or chemotherapy; | | | PBRT 80Gy: 10 (100%) Pulmonary: 7 (70%) CVD: 3 (30%) Severe DM: 1 (10%) Age: 0 Others: 0 PBRT 60 Gy: 18 (100%) Pulmonary: 6 (33%) CVD: 6 (33%) Severe DM: 4 (22%) Age: 2 (11%) Others: 2 (11%) |
| | | Exclusion criteria: NR | | | Performance status: NR |
| Lagerwaard-2011, Netherlands, #2122 | Study design: RET, SAS Patients enrolled: 177 (100%) Lost to FU/excluded/missing: 0 | Inclusion criteria: 1. Primary clinical stage I NSCLC 2. Medically operable Exclusion criteria: 1. GOLD COPD class 3-4 2. FEV1 < 50% of predicted 3. DLCO < 50% of predicted 4. WHO performance status ≥ 3 5. Major comorbidity (cardiac, renal) that precludes surgery | Stage I: 177 (100%) | Location: NR Histopathology: Hst confirmed: 60 (33%) ACC: 20 (33%) SCC: 16 (27%) NSCLC NOS: 24 (38%) Undiagnosed: 117 (66%) | Age (years): 76 (50-91) Women: 76 (43%) Race: NR Co-morbidities: GOLD COPD No COPD: 65 (37%) Class I: 37 (21%) Class II: 75 (42%) CCI score: 0: 18 (10%) 1: 59 (33%) 2: 38 (22%) 3: 39 (22%) 4: 16 (9%) 5: 7 (4%) Current or former smoker: 168 (95%) |
| Onishi-2011, Japan, #2802 (longer FU to | Study design: RET, SAS | Inclusion criteria: 1. Hst confirmed primary clinical stage I NSCLC | Stage I: 87 (100%) | Location: NR | Age (years): 74 (43-87) |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient characteristics |
|------------------------------|--|--|---------------------|--|--|
| Onishi-2007, Japan, #2803 | <p>Patients enrolled: 87 (100%)</p> <p>Lost to FU/excluded/missing: 0</p> | <p>2. Medically operable but refused surgery</p> <p>Exclusion criteria: NR</p> | | <p>Histopathology: Hst confirmed: 87 (100%) ACC: 54 (62%) SCC: 25 (29%) NSCLC NOS: 8 (9%)</p> | <p>Women: 24 (28%)</p> <p>Race: NR</p> <p>Co-morbidities: Chronic lung disease: 38 (44%)</p> <p>Performance status: ECOG 0: 51 (59%) 1: 30 (34%) 2: (7%)</p> |
| Shibamoto 2012, Japan, #4629 | <p>Study design: PRO, SAS</p> <p>Patients enrolled: Total: 180 (100%) Medically inoperable: 120 (67%) Refused surgery: 60 (33%)</p> <p>Lost to FU/excluded/missing: 0</p> | <p>Inclusion criteria: Histologically proven NSCLC stage 1 not suitable for surgery for medical or functional reasons</p> <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Tumor > 5 cm in greatest dimension 2. WHO PS < 2 or PS 3 when not due to pulmonary disease 3. Active concurrent cancer 4. FEV1/FVC < 60% or percentage vital capacity < 75% | Stage I: 180 (100%) | <p>Location: Not stated by operability</p> <p>Histopathology: Pathological confirmation: 180 (100%) Not stated by operability</p> | <p>Age (years): 77 (29-89) all cases</p> <p>Women: 57 (32%) all cases</p> <p>Race: NR</p> <p>Comorbidities: NR</p> <p>Performance status: WHO 0: 87 (48%) 1: 69 (38%) 2: 21 (12%) 3: 3 (2%) all cases</p> |
| Takeda-2009, Japan, #3700 | <p>Study design: RET, SAS</p> <p>Patients enrolled: Total: 63 (100%) Medically inoperable: 49 (78%) Operable: 14 (22%)</p> <p>Lost to FU/excluded/missing: 0</p> | <p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Primary clinical stage I NSCLC 2. WHO performance status ≤ 2 <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Prior radiation to lung or mediastinum | Stage I: 63 (100%) | <p>Location: NR</p> <p>Histopathology: Hst confirmed: 52 (82%) ACC: 35 (56%) SCC: 14: 22%) NOS: 3 (5%) Undiagnosed: 11 (18%)</p> | <p>Age: 78 (56-91)</p> <p>Women: 23 (36%)</p> <p>Race: NR</p> <p>Co-morbidities:</p> |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/exclusion criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient characteristics |
|-------|--|------------------------------|--------------------|---|---|
| | | | | | COPD, advanced age, other illnesses: 49 (78%) |
| | | | | | Performance status: WHO \leq 2: 63 (100%) |

Appendix Table C8. Outcomes and interventions of studies that address Key Question 2

| Study | Study Outcomes | Interventions |
|---------------------------------|---|---|
| <p>Chen-2012, #4554</p> | <p>Study Objective: To evaluate outcomes of SBRT in potentially operable patients with primary stage I NSCLC</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of outcomes: OS, LCT</p> <p>Cause of death: Total: 12 (30%) Unrelated to lung cancer: 10 (83%) Related to lung cancer: 2 (17%)</p> <p>Length of FU: Median 44 (12-72) mos</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Cyberknife (Acurray Inc., Sunnyvale, CA)</p> <p>Dose/frequency/details: Prescribed dose: 50 Gy (42-60 Gy) to the PTV 80% isodose line 3 frs Mean 7 days (5-11 days)</p> <p>Technical details: Beam energy NR</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria: PET/CT scans at 3 mos intervals after SBRT Biopsy required to confirm progression</p> |
| <p>Iwata-2010, #1747</p> | <p>Study Objective: To analyzed the safety and efficacy of high-dose proton therapy and carbon-ion therapy applied to stage I NSCLC</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of Outcome(s): OS, DSS, Local control, Toxicity</p> <p>Cause of death: NR</p> <p>Length of FU: All patients observed for a minimum of 1.5 years or until death. Median duration of follow-up was 35.5 (18-66) months for living pts & 30.5 (4-66) months for all pts.</p> | <p>Intervention name: PBRT</p> <p>Vendor name: Synchrotron (Mitsubishi Electric Corporation, Kobe, Japan 3-D Rx planning system ((FOCUS-M, CMS, St. Louis, Mo and Mitsubishi Electric Corporation)</p> <p>Dose/frequency/details: PBRT 80Gy: 20 fractions, BED 10(Gy): 112</p> <p>PBRT 60 Gy: 10 fractions BED 10(Gy): 96</p> <p>Technical details: Pts were treated with 150-MeV proton beams</p> <p>Treatment Intention: NR</p> <p>Follow-up and Evaluation Criteria:</p> |

| Study | Study Outcomes | Interventions |
|--|--|---|
| Lagerwaard-2011, #2122 | <p>Study Objective: To evaluate outcomes of SBRT in potentially operable patients with primary stage I NSCLC</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of outcomes: OS, LCT, toxicity</p> <p>Cause of death: Total: 34 (19%) Unrelated to lung cancer: 12 (35%) Related to lung cancer: 14 (41%) Unknown: 5 (15%)</p> <p>Length of FU: Median 32 mos</p> | <ul style="list-style-type: none"> • After Rx, pts FU at 1.5, 3, 4.5, 6, 9, and 12 months during the 1st yr, at intervals of 3 months in the 2nd yr, and at 6-month intervals in the 3rd yr. • CT, tumor marker, Brain MRI and FDG-PET were used to monitor tumor progression. • Local responses was assessed according to the modified WHO response evaluation criteria. • Toxicities were evaluated with the CTCAE version 3.0. • Medically inoperability defined as pts with poor pulmonary function (vital capacity <75% or ratio of FEV 1 to forced vital capacity <60%), a history of major CVD, severe DM, advanced age (80 years old), or other debilitating conditions that preclude surgery. <p>Intervention name: SBRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: Prescribed dose: 60 Gy to the PTV 80% isodose line BED: > 100 Gy for all fractionations 3, 5, or 8 frs 2 weeks</p> <p>Technical details: Beam energy NR</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria: CT scans at 3, 6, 12 mos after SBRT FDG PET only if relapse suspected Toxicity assessed (criteria NR)</p> |
| Onishi-2011, #2802 (longer FU to Onishi-2007, #2803) | <p>Study Objective: To evaluate high-dose SBRT for stage I NSCLC in patients who were medically operable but refused surgery</p> <p>Primary outcome: OS, CSS, LCT, toxicity</p> <p>Definition: NR</p> | <p>Intervention name: SBRT</p> <p>Vendor name: NR</p> <p>Dose/frequency/details: Prescribed dose: 45-72 Gy at the PTV isocenter BED: Median 116 (100-141) Gy 3-10 frs</p> |

| Study | Study Outcomes | Interventions |
|-----------------------------------|--|---|
| | <p>Secondary outcome(s): NR</p> <p>Definitions: NA</p> <p>List of outcomes: OS, CSS, LCT, toxicity</p> <p>Cause of death: NR</p> <p>Length of FU: Median 55 mos</p> | <p>Consecutive days or every other day</p> <p>Technical details: 4- and 6-MeV beam energy</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria: First FU at 4 weeks, then every 1-3 mos thereafter Chest CT scans every 3 mos for first year then every 4-6 mos thereafter Toxicity assessed according to CTCAE v.2.0</p> |
| <p>Shibamoto -2012, #4629</p> | <p>Study Objective: To report a multi-institutional study of SBRT in inoperable and operable patients with histologically confirmed stage I NSCLC</p> <p>Primary outcome: LC at 3-years follow-up</p> <p>Definition: Calculated from the start of SBRT</p> <p>Secondary outcome(s): OS, CSS</p> <p>Definitions: Calculated from the start of SBRT</p> <p>List of Outcome(s): OS, CSS, LCT, Toxicity</p> <p>Cause of death: Dead: 65 (36%) NR by operability</p> <p>Length of FU: 36 months NR by operability</p> | <p>Intervention name: SBRT</p> <p>Vendor name: Novalis image-guided system (Varian Medical Systems, Palo Alto, CA) CLINAC 23EX or 21 EXS (Varian)</p> <p>Eclipse v.7.5.14.3 (Varian) BRAINSCAN v.5.31 (BrainLAB, Feldkirchen, Germany) Pinnacle3 (Philips, Madison, WI)</p> <p>Dose/frequency/details: Hypofractionated SBRT Total dose: 44-52 Gy to 90% of the isodose line of PTV in 4 frs for 9-21 days</p> <p>Technical details: 6-MV photons</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> All time intervals were calculated from the start of SBRT CT scans of chest and upper abdomen at 2-months intervals up to 6 months, every 2-4 months thereafter Toxicity: CTCAE v3.0 criteria during and up to 3 months after RT |
| <p>Takeda-2009, #3700</p> | <p>Study Objective: To analyze clinical outcomes of SBRT for patients with stages IA and IB NSCLC</p> <p>Primary outcome: NR</p> <p>Definition: NA</p> <p>Secondary outcome(s):</p> | <p>Intervention name: SBRT</p> <p>Vendor name: XiO treatment planning system, V.4.2 or v.4.3, CMS, St. Louis, MO</p> <p>Linear accelerator NR</p> <p>Dose/frequency/details: Prescribed dose: 50 Gy to the 80% isodose line 10 Gy per fraction</p> |

| Study | Study Outcomes | Interventions |
|-------|--|--|
| | <p data-bbox="310 131 352 155">NR</p> <p data-bbox="310 185 447 237">Definitions: NA</p> <p data-bbox="310 266 558 318">List of outcomes: OS, CSS, LCT, toxicity</p> <p data-bbox="310 347 495 399">Cause of death: NR</p> <p data-bbox="310 428 478 480">Length of FU: 31 (10-72) mos</p> | <p data-bbox="1140 131 1255 155">5 fractions</p> <p data-bbox="1140 185 1339 237">Technical details: Beam energy NR</p> <p data-bbox="1140 266 1373 318">Treatment Intention: Curative</p> <p data-bbox="1140 347 1530 371">Follow-up and Evaluation Criteria:</p> <ul data-bbox="1140 380 1969 509" style="list-style-type: none"> <li data-bbox="1140 380 1608 404">• Monthly for first 6 mos, with chest X-ray <li data-bbox="1140 407 1969 459">• CT scans at 1 and 3 mos after SBRT, then at 3-mos intervals during first 2 years <li data-bbox="1140 462 1835 487">• FU interviews and CT scans at 4-6 mos intervals after 2 years <li data-bbox="1140 490 1654 514">• Toxicity assessed according to CTCAE v.3.0 |

Appendix Table C9. Survival and local control outcomes of studies that address Key Question 2

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|--|--|--|--|---|-----|
| Chen-2012, #4554 | SBRT Overall survival: Median ~60 mos 3-years: 75% Cancer specific survival: NR | SBRT Overall survival NA Cancer specific survival: NA | SBRT Local control: 95% at follow-up | Local control: NA | No |
| Iwata-2010, # 1747 | Overall survival: 3-years: 80% Cancer/disease specific survival: NR | Overall survival: NA Cancer/disease specific survival: NA | Local control: NR | Local control: NA | Yes |
| Lagerwaard-2011, #2122 | SBRT Overall survival: Median 62 mos 1-year: 95% 3-years: 85% 5-years: 51% (only 10 pts at risk) Cancer specific survival: NR | SBRT Overall survival: NA Cancer specific survival: NA | SBRT Local control: 1-year: 98% 3-years:93% | Local control: NA | No |
| Onishi-2011, #2802 (longer FU to Onishi-2007, #2803) | SBRT Overall survival: 5-years: 70% (95% CI: 59-86%) Cancer specific survival: 5-years: 76% (95% CI: 66-86%) | SBRT Overall survival: NA Cancer specific survival: NA | SBRT Local control: 5-years: 87% (95% CI: 84-100%) | Local control: NA | No |
| Shibamoto 2012, #4629 | SBRT: Overall survival: Median: Not reached 3-years: 74% 5-years: 70% Cancer/disease specific survival: NR by operability | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: NR by operability | Local control: NA | No |
| Takeda-2009, #3700 | SBRT Overall survival: 3-years: 90% (stage IA) 3-years: 63% (stage IB) p = 0.09 3-years: 91% (operable) Cancer/disease specific | Overall survival: NA Cancer/disease specific survival: NA | SBRT Local control: 3-years: 93% (stage IA) 3-years: 96% (stage IB) p = 0.86 | Local control: NA | No |

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|-------|--|--|---|---|-----|
| | survival: 3-years: 100% (stage IA) 3-years: 81% (stage IB) $p = 0.10$ 3-years: 91% (operable) | | | | |

Appendix Table C10. Miscellaneous outcomes of studies that address Key Question 2

| Study | Intervention Group 1 | Intervention Group 2 |
|--|--|--|
| Chen-2012, #4554 | SBRT Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | SBRT Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Iwata-2010, # 1747 | PBRT Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | PBRT Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Lagerwaard 2011, #2122 | SBRT Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | SBRT Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Onishi-2011, #2802 (longer FU to | SBRT Lung function: NR | SBRT Lung function: NA |

| Study | Intervention Group 1 | Intervention Group 2 |
|---------------------------|--|---|
| Onishi-2007, #2803) | Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Shibamoto- 2012, #4629 | SBRT: Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| Takeda-2009, #3700 | SBRT Lung function: NR Obstructive symptoms: NR Quality of life: NR Performance status: NR Others: NR | SBRT Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |

Appendix Table C11. Toxicity outcomes of studies that address Key Question 2

| Study | Intervention Group 1 | Intervention Group 2 |
|--|---|----------------------|
| Chen-2012, #4554 | SBRT NR | NA |
| Iwata-2010, #1747 | PBRT 60 Gy: RP Grade 2: 4 (10.8%) RP Grade 3: 0 Dermatitis Grade 2: 4 (10.8%) Dermatitis Grade 3: 0 Rib fracture Grade 2: 6 (16.2%) Soft Tissue Grade 2: 2 (5.4%) PBRT 80Gy: RP Grade 2: 3 (15.0%) RP Grade 3: 1 (5.0%) Dermatitis Grade 2: 4 (20.0%) Dermatitis Grade 3: 3 (15.0%) Rib fracture Grade 2: 9 (45.0%) Soft Tissue Grade 2: 2 (10.0%) | NA |
| Lagerwaard-2011, #2122 | SBRT 30-day mortality: 0 (0%) Grade > 3 pneumonitis: 4 (2%) Rib fracture: 5 (3%) | NA |
| Onishi-2011, #2802 (longer FU to Onishi-2007, #2803) | SBRT Grade 2 pulmonary: 4 (5%) Grade 3 pulmonary: 1 (1%) Grade 3 dermatitis: 3 (3%) Grade 3 esophagitis: 1 (1%) Rib fracture: 4 (5%) | NA |
| Shibamoto-2012, #4269 | SBRT: NR by operability | NA |
| Takeda-2009, #3700 | SBRT No acute toxicity was observed Grade 2 pneumonitis: 1 (2%) Grade 3 pneumonitis: 2 (3%) Grade 5 bacterial pneumonia at site of Grade 3 radiation pneumonitis: 1 (2%) | SBRT NA |

Appendix Table C12. Attributes of studies that address Key Question 2

| ID | HC | Enroll Start | Enroll Date | Design | Study Setting | Treatment Setting | Institution Setting(s) | Stage(s) | Staging Criteria | COI | Funding |
|-------------------------|---------|--------------|-------------|--------|---------------|-------------------|------------------------|----------|------------------|-----|---------|
| Chen-2012, #4554 | Y | 11/04 | 11/09 | PRO | SI | NR | TH | I | NR | N | NR |
| Iwata, 2010, #1747 | Yes | 04/03 | 04/07 | PRO | SI | NR | TH | I | IUAC 2002 | N | G |
| Lagerwaard, 2011, #2122 | N (66%) | 04/03 | 12/10 | RET | SI | O | TH | I | NR | Y | NR |
| Onishi, 2011, #2802 | Yes | 04/95 | 03/04 | RET | M | NR | TH | I | NR | N | G |
| Shibamoto – 2012, #4269 | Y | 05/04 | 11/08 | PRO | M | NR | TH | I | IUAC2002 | N | NR |
| Takeda, 2009, #3700 | N (17%) | 12/01 | 05/07 | RET | M | NR | TH, CH | I | NR | N | NR |

Appendix Table C13. Description of studies that address Key Question 3

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/Exclusion Criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|-------------------------------|---|---|--|---|--|
| Allison-2004, USA, #108 | <p>Study design: SAS, PRO</p> <p>Patients enrolled: Total: 10 (100%)</p> <p>Lost to FU/excluded/missing: None</p> | <p>Inclusion criteria: Not reported, paraphrased 1. Patients with symptomatic endobronchial recurrence 2. Non responsive to multiagent chemo and RT for initial stage III NSCLC</p> <p>Exclusion criteria: Not reported</p> | All patients had recurrent endobronchial obstruction subsequent to stage III NSCLC | <p>Location: ML: 2 (20%) UL: 3 (30%) LL: 3 (30%) MS: 2 (20%)</p> <p>Histopathology: AC: 8 (80%) SCC: 2 (20%)</p> | <p>Age: 65.9 (±8.4) 66.5 (52-77)</p> <p>Women: 2 (20%)</p> <p>Race: Not reported</p> <p>Co-morbidities: Not reported</p> <p>Performance status: Baseline KPS: 45 (±7.1) Post Rx KPS: 77 (±9.5)</p> |
| Chella-2000, Italy, #654 | <p>Study design: RCT, PRO</p> <p>Patients enrolled: Total: 29 (100%) YAGL + BCHY: 14 (48%) YAGL: 15 (52%)</p> <p>Lost to FU/excluded/missing: None</p> | <p>Inclusion criteria: 1. NSCLC involving central airway & not eligible for further surgical, chemotherapeutic or external beam RT 2. An expectation of life of at least 2 months 3. A performance status score (WHO) ≤ 2</p> <p>Exclusion criteria: Not reported</p> | Not reported | <p>Location: Trachea: 6 (21%) Carina & both main stems: 6 (21%) Carina & one main stem: 7 (24%) One main stem: 7 (24%) Lobar bronchus: 3 (10%)</p> <p>Histopathology: Total: SCC: 21 (72%) AC: 6 (21%) LCC: 2 (7%) YAGL + BCHY: SCC: 11 (79%) AC: 2 (14%) LCC: 1 (7%) YAGL: SCC: 10 (67%) AC: 4 (27%) LCC: 1 (7%)</p> | <p>Age: 61 (47-76) (note this is mean with range)</p> <p>Women: 6 (21%)</p> <p>Race: Not reported</p> <p>Co-morbidities: Not reported</p> <p>Performance status: Total: WHO 0: 3 (10%) I: 11 (40%) II: 15 (52%) YAGL + BCHY: 0: 1 (7%) I: 4 (29%) II: 9 (64%) YAGL: 0: 2 (13%) I: 7 (47%) II: 6 (40%)</p> |
| Celebioglu-2002, Turkey, #604 | <p>Study design: SAS, RET</p> <p>Patients enrolled:</p> | <p>Inclusion criteria: 1. Had inoperable lung cancer, proven histologically,</p> | <p>Stage IIIB: 83 (87%) Stage IV: 12 (13%)</p> | <p>Location: Central: 79 (83%) Peripheral: 16 (17%)</p> | <p>Age: 60 (±7, 41-81) (note this is mean with SD & range)</p> |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/Exclusion Criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|---------------------------------|---|--|--|---|--|
| | BCHY Total: 95 (100%) Lost to FU/excluded/missing: Not reported | 2. Had endobronchial tumor, visualized via bronchoscope, 3. Were inoperable 4. Were not subjected to standard Rx regimes because of ≥ 1 severe symptoms or recurrence after definitive Rx. Exclusion criteria: Not reported | | Histopathology: SCC: 59 (62%) NSCC: 36 (38%) | Women: Female: 7 (7%) Race: Not reported Co-morbidities: Not reported Performance status: ECOG (baseline) 1: 14 (15%) 2: 61 (64%) 3: 17 (18%) 4: 3 (3%) |
| Celikoglu-2006, Turkey, #606 | Study design: SAS, PRO Patients enrolled: Total: 23 (100%) No of obstructions: 28 (100%) Lost to FU/excluded/missing: None | Inclusion criteria: 1. Patients presenting with obstruction of trachea or of a major bronchus secondary to inoperable hst cnf NSCLC 2. Near complete obstruction (quantified by $\geq 50\%$ occlusion of at least 1 major airway) 3. Disease confined to one hemithorax and without distant metastases Exclusion criteria: 1. Patients requiring irradiation for palliative purposes 2. Patients with small cell carcinoma | Stage IIIA: 9 (39%) Stage IIB: 14 (61%) | Location: MB: 14 (48%) BI: 2 (7%) UL: 4 (14%) LL: 2 (7%) Carina, MB: 3 (10%) Trachea: 4 (14%) Histopathology: SCC: 19 (83%) AC: 3 (13%) SCC: 1 (4%) (poorly differentiated) | Age: 56.8 (± 8.5 , 43-78) (note this is mean with SD & range) Women: 3 (17%) Race: Not reported Co-morbidities: Not reported Performance status: Not reported |
| Chhajed-2006, Switzerland, #696 | Study design: SAS, RET Patients enrolled: Total: 144 (100%) STNT or LASR: 52 (36%) Laser only: 13 (25%) Stent only: 13 (25%) Both: 26 (50%) Lost to FU/excluded/missing: | Inclusion criteria: 1. Central airway obstruction treated with therapeutic bronchoscopy (laser with or without stent insertion) 2. Chemotherapy 3. Eligible for radiotherapy Exclusion criteria: 1. Untreated central airway | Not reported | Location: Not reported Histopathology: SCC: 25 (48%) AC: 14 (27%) LCC: 4 (8%) Not specified: 9 (17%) | Age: 61 (mean age, SD or range Not reported) Women: 14 (27%) Race: Not reported Co-morbidities: Not reported |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/Exclusion Criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|-----------------------------|---|--|--|--|--|
| | Not reported | obstruction, or 2. Central airway obstruction treated with therapeutic bronchoscopy but not received chemotherapy | | | Performance status: Not reported |
| Guilcher-2011, France, #188 | Study design: SAS, RET Patients enrolled: BCHY: 226 (100%) Lost to FU/excluded/missing: Not reported | Inclusion criteria: 1. Hst proven NSCLC, endobronchial carcinomas only, 2. Normal CT, 3. No metastases Contraindication to surgical removal and EBRT, 4. Can undergo diazepam-induced analgesia Exclusion criteria: 1. Visible extrabronchial extension on CT scan 2. Use of HDR brachytherapy as a boost after EBRT or to treat an endobronchial recurrence of a previously treated tumor | Tis: 60 (27%) T1: 153 (68%) T2: 9 (4%) Unknown: 4 (1%) | Location: Proximal: 21 (9%) Distal: 200 (89%) Unknown: 5 (2%) Histopathology: SCC: 217 (96%) AC: 5 (2%) Others: 4 (2%) | Age: 62.2 (40-84) (Note this is mean age with range) Women: 3 (1%) Race: Not reported Co-morbidities: Not reported Performance status: Not reported |
| Jimenez-1999, Spain, #978 | Study design: RCT, PRO Patients enrolled: Total: 31 (100%) PHDT: 14 YAGL: 17 Lost to FU/excluded/missing: Not reported | Inclusion criteria: 1. >18 yrs of age 2. Nonpregnant, infertile or postmenopausal females. 3. Biopsy-proven or recurrent inoperable NSCLC with totally or partially obstructive endobronchial lesions with or without extrabronchial tumor 4. Clinical evidence of airway obstruction 5. KPS \geq 40% 6. Ability to tolerate bronchoscopic procedures 7. \geq 4 weeks from the last chemotherapy cycle and \geq 3 weeks from the last radiation dose | PHDT: 14 (100%) Stage I: 3 (21%) Stage II: 1 (7%) Stage III: 5 (36%) Stage IV: 3 (21%) Recurrent: 2 (14%) YAGL: 17 (100%) Stage I: 1 (6%) Stage II: 0 Stage III: 11 (65%) Stage IV: 4 (24%) Recurrent: 1 (6%) | Location: Total: 31 (100%) MB: 20 (65%) SB: 8 (26%) IB: 3 (10%) Histopathology: PHDT: 14 (100%) SCC: 13 (93%) AC: 1 (7%) Undifferentiated: 0 YAGL: 17 (100%) SCC: 12 (71%) AC: 2 (12%) Undifferentiated: 3(18%) | Age: Total: 64 (\pm 7) PHDT: 67 (Mean) YAGL: 64 (Mean) Women: PHDT: 0 YAGL: 0 Race: Not reported Co-morbidities: Not reported Performance status: Quantitative numbers not reported but stated that KPS was similar b/w groups |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/Exclusion Criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|-------------------------------------|--|---|--|---|---|
| Jones-2001, USA, #1862 | <p>Study design: SAS, RET</p> <p>Patients enrolled: Total: 10 (100%)</p> <p>Lost to FU/excluded/missing: None</p> | <p>Exclusion criteria: 1. Previously undergone PHDT or YAGL resection 2. had tracheal lesions that compromised both main bronchi, brain metastasis, bone pain due to skeletal metastasis, pneumonectomy, tumors eroding or invading great vessels, haematoporphyrin hypersensitivity, leukocyte count $< 2 \times 10^9$ cells.L⁻¹, platelet count $< 100 \times 10^9$ cells L⁻¹, coagulation time ≥ 15 min, renal failure or liver dysfunction</p> <p>Inclusion criteria: 1. Patients diagnosed with stage III/IV obstructive NSCLC 2. Patients who underwent PHDT</p> <p>Exclusion criteria: Not reported</p> | <p>Stage III: 4 (40%) Stage IV: 6 (60%)</p> | <p>Location: Total: 17 (100%) MS: 5 (29%) Trachea: 3 (18%) LL: 4 (24%) ML: 2 (12%) UL: 1 (6%) BI: 2 (12%)</p> <p>Histopathology: AC: 7 (70%) Adenoid cystic: 1 (10%) Carcinoma: 2 (20%)</p> | <p>Age: 67 (± 8.8, 48-76) (SD was calculated)</p> <p>Women: 3 (30%)</p> <p>Race: Not reported</p> <p>Co-morbidities: Not reported</p> <p>Performance status: Not reported</p> |
| Langendjik-2001, Netherlands, #2144 | <p>Study design: RCT, PRO</p> <p>Patients enrolled: Total: 95 (100%) EBRT +BCHY: 47 (49%) EBRT: 48 (51%)</p> <p>Lost to FU/excluded/missing: 98 randomized, 3 were excluded because they did not fulfill eligibility criteria. Further, 5 patients out of 95 did not complete baseline QOL assessments and were excluded from QOL analysis.</p> | <p>Inclusion criteria: 1. Have biopsy proven NSCLC, stage I, II, III 2. Endobronchial tumor in the proximal main bronchus or lobar bronchus 3. WHO performance status 0 to 3 4. No prior or planned chemo, prior surgery, prior radiotherapy, other malignancies, pleuritis carcinomatosa, distant mets or superior vena cava syndrome.</p> | <p>EBRT +BCHY Stage I: 4 (9%) Stage III: 43 (91%)</p> <p>EBRT Stage I: 5 (10%) Stage III: 43 (90%)</p> | <p>Location: EBRT +BCHY UL: 28 (58%) ML: 4 (8%) LL: 6 (13%) MB: 9 (19%)</p> <p>EBRT UL: 21 (44%) ML: 4 (8%) LL: 10 (21%) MB: 13 (27%)</p> <p>Histopathology: Not reported</p> | <p>Age: EBRT +BCHY: 67 (± 9) EBRT: 68 (± 9)</p> <p>Women: EBRT +BCHY: 9 (19%) EBRT: 8 (17%)</p> <p>Race: Not reported</p> <p>Co-morbidities: Not reported</p> <p>Performance status: Total</p> |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/Exclusion Criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|--|---|---|--|--|--|
| | | Exclusion criteria: 1. Prior Rx with Neodymium-YAG laser 2. Patients with a complete obstruction 3. Patients requiring ≥ 2 catheters | | | 0: 23 (24%) 1: 54 (57%) 2: 13 (14%) 3: 5 (5%) EBRT +BCHY 0: 11 (23%) 1: 26 (55%) 2: 8 (17%) 3: 2 (4%) EBRT 0: 12 (25%) 1: 28 (58%) 2: 5 (10%) 3: 3 (6%) |
| Lencioni-2008, Multiple Countries, #2238 | Study design: SAS, PRO Patients enrolled: Total: 106 (100%) NSCLC: 33 (31%) Lost to FU/excluded/missing: Not reported but outcomes reported for 22 patients. Unknown as to how many patients contributed to OS data. | Inclusion criteria: 1. Age > 18 yrs; 2. Biopsy-proven NSCLC or lung mets; 3. Patients rejected for surgery & considered unfit for RT or chemo; 4. Up to 3 tumors/lung, each 3-5 cm or smaller in greatest diameter, detected by CT; 5. Tumors located at least 1 cm from trachea, main bronchi, esophagus, aorta, aortic arch branches, main, right, or left pulmonary artery and heart; 6. Tumors accessible by percutaneous route; 7. ECOG performance status of 0, 1, or 2; 8. Platelet count $>100 \times 10^9$ /L; 9. INR ≤ 1.5 . Exclusion criteria: 1. Previous pneumonectomy; 2. Patients considered high-risk for RFA because of major comorbid medical | Stage I: 13 (39%) Recurrent: 20 (61%) | Location: Not reported Histopathology: SCC: 18 (55%) AC: 13 (29%) BC: 1 (3%) LCC: 1 (3%) | Age: 66.5 (11.1) 67 (29-82) Women: 8 (24%) Race: Not reported Co-morbidities: Not reported Performance status: Not reported |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/Exclusion Criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|--------------------------|---|--|--------------------|---|---|
| Moghissi-1999, UK, #2591 | <p>Study design: RCT, PRO</p> <p>Patients enrolled: Total: 75 (100%) EBRT: 38 (51%) EBHT: 37 (49%)</p> <p>Lost to FU/excluded/missing: 16 excluded</p> | <p>conditions 3. Tumors associated with atelectasis or obstructive pneumonitis; 4. Renal failure needing hemo or peritoneal dialysis; 5. Active clinically serious infection; 6. History of organ allograft; substance abuse or any medical, psychological, or social conditions that might interfere with the patients participation in the study or assessment of the study findings</p> <p>Inclusion criteria: 1. No previous thoracic RT 2. Partial obstruction of trachea or partial or complete obstruction of bronchus or a lobar bronchus 3. Microscopically confirmed NSCLC 4. Locally too advanced for surgical resection or radical RT.</p> <p>Exclusion criteria: Not reported</p> | Not reported | <p>Location: EBRT: Trachea: 1 (3%) MB: 22 (53%) Others: 15(39%)</p> <p>EBHT: Trachea: 1 (3%) MB: 21 (57%) Others: 1 (41%)</p> <p>Histopathology: Not reported</p> | <p>Age: EBRT: 72 EBHT: 71 (Note these are median age)</p> <p>Women: EBRT: 15 (39%) EBHT: 13 (35%)</p> <p>Race: Not reported</p> <p>Co-morbidities: Not reported</p> <p>Performance status: EBRT (WHO PS): 0: 3 (8%) 1: 16 (42%) 2: 14 (37%) 3: 5 (13%) EBHT (WHO PS): 0: 2 (1%) 1: 16 (43%) 2: 14 (38%) 3: 5 (14%)</p> |
| Muto-2000, Italy, #2665 | <p>Study design: SAS, PRO</p> <p>Patients enrolled: Total: 320 (100%) BCHY (10 Gy): 84 (26%)</p> | <p>Inclusion criteria: 1. Histological proven NSCLC 2. Stage IIIA-IIIB 3. KPS > 6 4. Life expectancy > 6</p> | Not reported | <p>Location: Not reported</p> <p>Histopathology: Not reported</p> | <p>Age: Not reported</p> <p>Women: Not reported</p> |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/Exclusion Criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|------------------------------------|---|--|---|--|---|
| | <p>BCHY (14Gy) + EBRT: 47 (15%) BCHY (15Gy, 1cm) + EBRT: 50 (16%) BCHY (15Gy, 0.5 cm) + EBRT: 139 (43%)</p> <p>Lost to FU/excluded/missing: LTFU: 40 (13%) Evaluable patients: BCHY (10 Gy): 78 (28%) BCHY (14Gy) + EBRT: 46 (16%) BCHY (15Gy, 1cm) + EBRT: 36 (13%) BCHY (15Gy, 0.5 cm) + EBRT: 120 (43%)</p> | <p>months</p> <p>5. Presence of cough and/or dyspnea, hemoptysis, obstructive pneumonia</p> <p>6. No chemo before or after RT</p> <p>Exclusion criteria: Not reported</p> | | | <p>Race: Not reported</p> <p>Co-morbidities: Not reported</p> <p>Performance status: Not reported</p> |
| Mallick-2006, India, #2417 | <p>Study design: PRO, RCT</p> <p>Patients enrolled: Total: 45 (100%) EBRT + BCHY-16Gy: 15 (33.3%) EBRT + BCHY-10Gy: 15 (33.3%) BCHY-15Gy: 15 (33.4%)</p> <p>Lost to FU/excluded/missing: None</p> | <p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Previously untreated, inoperable, locally advanced NSCLC patients. 2. Endoscopically proven endobronchial disease with ≥ 1 symptom (dyspnea, cough, hemoptysis or obstructive pneumonia) 3. KPS score between 60 to 80 <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Previously Rx patients 2. Those with mets who would require primary chemo. | Stage III: 45 (100%) | <p>Location:</p> <p>EBRT+BCHY-16Gy: 15 MB: 6 (40%) LB: 9 (60%)</p> <p>EBRT+BCHY-10Gy: 15 MB: 6 (40%) LB: 9 (60%)</p> <p>BCHY-15Gy: 15 MB: 8 (53%) LB: 7 (47%)</p> <p>Histopathology:</p> <p>EBRT+BCHY-16Gy: 15 SCC: 13 (87%) AC: 1 (7%) LCC: 1 (7%)</p> <p>EBRT+BCHY-10Gy: 15 SCC: 13 (87%) AC: 2 (13%)</p> <p>BCHY-15Gy: 15 SCC: 14 (93%) AC: 1 (7%)</p> | <p>Age: Total: 64.5 (35-75) EBRT+BCHY-16Gy: 68.9 (45-75) EBRT+BCHY-10Gy: 63.1 (46-70) BCHY-15Gy: 61.5 (35-70) (Age is in mean)</p> <p>Women: Total: 2 (4%) EBRT+BCHY-16Gy: 0 EBRT+BCHY-10Gy: 1 (7%) BCHY-15Gy: 1 (7%)</p> <p>Race: Not reported</p> <p>Co-morbidities: Not reported</p> <p>Performance status: Not reported</p> |
| Petera-2001, Czech Republic, #2914 | <p>Study design: SAS, PRO</p> <p>Patients enrolled: Total: 67 (100%) BCHY (Cur): 20 (30%) BCHY (Pall): 21 (31%)</p> | <p>Inclusion criteria:</p> <p>BCHY (Cur):</p> <ol style="list-style-type: none"> 1. Inoperable LC with WHO PS 0 to 2 2. Without wt loss >10% in previous 6 months | <p>BCHY (Cur):</p> <p>Stage II: 2 (10%) Stage III: 16 (80%) Stage IV: 1 (5%) Other: 1 (5%)</p> <p>BCHY (Pall);</p> | <p>Location:</p> <p>BCHY (Cur): MS: 6 (30%) Lobar bronchus: 9 (45%) > 1 location: 5 (25%) BCHY (Pall): MS: 5 (24%)</p> | <p>Age: BCHY (Cur): 59 (46-75) BCHY (Pall): 63 (49-83) (Note: This is mean with range)</p> <p>Women:</p> |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/Exclusion Criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|-----------------------------------|--|--|---|--|---|
| | Lost to FU/excluded/missing: BCHY (Pall): 1 (1%) | BCHY (Pall): 1. Advanced disease 2. Poor performance status 3. With wt loss >10% in previous 6 months Exclusion criteria: Not reported | Stage III: 16 (76%) Stage IV: 3 (14%) Other: 2 (10%) | Lobar bronchus: 11 (52%) > 1 location: 5 (24%) Histopathology: BCHY (Cur): SC: 18 (90%) AC: 1 (5%) NSCLC unspec: 1 (5%) BCHY (Pall): SC: 19 (90%) AC: 1 (5%) NSCLC unspec: 1 (5%) | BCHY (Cur): 0 (0%) BCHY (Pall): 3 (14%) Race: Not reported Co-morbidities: Not reported Performance status: Not reported |
| Stout-2000, UK, #3640 | Study design: RCT, PRO Patients enrolled: Total: 108 (100%) BCHY: 49 (49%) EBRT: 50 (51%) Lost to FU/excluded/missing: 9 (8%) excluded- relapsed after surgery | Inclusion criteria: 1. Thoracic symptoms limited to cough, hemoptysis or breathlessness 2. fit to undergo therapeutic bronchoscopy or fractionated EBRT (WHO PS 0 to 2) 3. no clinical evidence of malignant disease beyond thorax 4. histologically confirmed NSCLC medically operable Exclusion criteria: Not reported | Not reported | Location: Not reported Histopathology: SCC: 81 (82%) | Age: 68 (40-84) Note this is mean) Women: 20 (20%) Race: Not reported Co-morbidities: Not reported Performance status: WHO BCHY: 2: 8 (16%) 3: 3 (6%) NR: 32 (78%) EBRT: 2: 13 (27%) 3: 4 (8%) NR: 32 (65%) |
| van Boxem-1999, Netherlands, #427 | Study design: NRC, RET Patients enrolled: Total: 31 (100%) YAGL: 14 (45%) ECAU: 17 (55%) | Inclusion criteria: 1. Patients had centrally located inoperable NSCLC and underwent bronchoscopic Rx because of dyspnea due to tracheobronchial obstruction caused by | YAGL Stage IV: 6 (43%) Stage IIIB: 6(43%) Stage IIIA: 2 (14%) ECAU Stage IV: 6 (35%) Stage IIIB: 10 (59%) | Location: YAGL Trachea: 3 (21%) Bronchi: 11 (79%) ECAU Trachea: 3 (18%) Bronchi: 14 (82%) | Age: YAGL: 61 (37-88) ECAU:62 (47-79) Women: YAGL: 3 (21%) ECAU: 7 (41%) |

| Study | Study design, enrollment numbers and lost to FU/excluded | Inclusion/Exclusion Criteria | Stage Distribution | Tumor/Obstruction Location & Histopathology | Patient Characteristics |
|-----------------------------------|--|--|---|---|--|
| | Lost to FU/excluded/missing: Total: 0 YAGL: 0 ECAU: 0 | intraluminal tumor Exclusion criteria: Not reported | Stage IIIA: 1 (6%) | Histopathology: YAGL AC: 1 (7%) SCC: 10 (71%) LCC: 3 (21%) ECAU AC: 5 (29%) SCC: 4 (24%) LCC: 8 (47%) | Race: YAGL: Not reported ECAU: Not reported Co-morbidities: YAGL: Not reported ECAU: Not reported Performance status: YAGL: Not reported ECAU: Not reported |
| Vucicevic-1999, Yugoslavia, #4010 | Study design: SAS, RET Patients enrolled: Total: 39 (100%) Lost to FU/excluded/missing: Not reported | Inclusion criteria: 1. Inoperable, occlusive histologically confirmed stage IIIB NSCLC Exclusion criteria: Not reported | Stage III: 39 (100%) | Location: Not reported Histopathology: AC: 2 (5%) SCC: 37 (95%) | Age: 60.6 (42-75) Women: 2 (5%) Race: Not reported Co-morbidities: Not reported Performance status: KPS: Range was 70-100% |
| Weinberg-2010, USA, #4066 | Study design: SAS, RET Patients enrolled: Total: 9 (100%) Lost to FU/excluded/missing: None | Inclusion criteria: 1. Patients received PHDT & HDR BCHY for endobronchial tumors Exclusion criteria: Not reported | I/II: 1 (11%) II: 1 (11%) III: 6 (67%) IV: 1 (11%) | Location: UL: 7 (29%) LL: 4 (17%) ML: 1 (4%) MS: 5 (21%) BI: 2 (8%) Trachea: 1 (4%) Lymph node: 2 (8%) Hilum: 1 (4%) Lingual: 1 (4%) Histopathology: SCC: 9 (100%) | Age: (52-73) Women: 1 (11%) Race: Not reported Co-morbidities: Not reported Performance status: Not reported |

Appendix Table C14. Outcomes and interventions of studies that address Key Question 3

| Study | Study Outcomes | Interventions |
|--------------------|--|--|
| Allison-2004, #108 | Study Objective: Authors reported in a case series fashion outcomes of 10 patients with symptomatic endobronchial | Intervention name: Stenting plus HDR brachytherapy |

| Study | Study Outcomes | Interventions |
|-------------------|--|---|
| | <p>recurrence who underwent 2 simultaneous interventions: stenting and HDR brachytherapy</p> <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): Local control, OS</p> <p>Cause of death: Progression of LC: 10 (100%)</p> <p>Length of FU: Not reported</p> | <p>Vendor name: Self-expanding metallic stent (Nitinol/Ultraflex, Boston Scientific Co., Natick, MA)</p> <p>Dose/frequency/details: 6 Gy was delivered to 0.5-cm depth via a Nucletron HDR for brachytherapy. Two additional HDR Rx were delivered at weekly intervals for a total dose of 18 Gy.</p> <p>Technical details: Flexible bronchoscope was used to place stent and simultaneously an HDR catheter was introduced.</p> <p>Treatment Intention: Palliative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Patients underwent bronchoscopy at each HDR and FU bronchoscope 1 & 3 months after the last HDR Rx, as well as when clinically indicated. • Biopsy was taken 1 or 3 months after the last HDR Rx. • All patients were FU to progression or death |
| Chella-2000, #654 | <p>Study Objective: To compare the efficacy of the combined Nd-YAG laser: HDR brachytherapy versus bronchial debulking with Nd-YAG laser alone in a prospective randomized study treatment.</p> <p>Primary outcome: Disease progression free period Definition: Not reported</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): Further endoscopic Rxs, median survival, PFT, blood gas analysis, Speiser's index</p> <p>Cause of death: Dead: 18 (62%) Local progression: 13 (72%) Distant mets: 5 (28%)</p> <p>Length of FU: Median FU: 17.8 months (9–35)</p> | <p>Intervention name: Laser and HDR brachytherapy</p> <p>Vendor name: Rigid bronchoscope (Wolf or Effer –Dumon) Catheter for BCHY (Nucletron)</p> <p>Dose/frequency/details: YAGL: Energy of 25–45 W, using pulses up to 1.2 s, was used for a mean total amount of 1850 J (range 1400–2200 J) BCHY: HDR brachytherapy 15–18 days after Nd-YAG laser debulking. High radioactive Iridium-192 source (10 Ci), prescribed dose was 5 Gy at 0.5 cm, with a total exposition time variable from 10 to 15 min. Rx was repeated 3 times every 7 days for a total dose of 15 Gy.</p> <p>Technical details: None</p> <p>Treatment Intention: Not reported</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Pulmonary function tests; arterial blood gas assessment; chest radiograph; fiberoptic bronchoscopy at baseline, 14 days after the laser debulking and from 30 to 45 days after HDR brachytherapy • A radiological (chest film and CT scan) and endoscopic followup |

| Study | Study Outcomes | Interventions |
|-----------------------|---|---|
| Celebioglu-2002, #604 | <p>Study Objective: To compare the palliation improvement pre- and post-radiotherapy.</p> <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): Symptom control, toxicity</p> <p>Cause of death: Not reported</p> <p>Length of FU: Surviving patients FU for a minimum of 3 months with a mean of 7.5±5.4 months</p> | <p>performed every 2 months.</p> <ul style="list-style-type: none"> Airway obstruction grade was calculated according to Speiser's obstruction score method Intraluminal radiotherapy associated morbidity was assessed according to Gollins's scoring system <p>Intervention name: HDR brachytherapy</p> <p>Vendor name: 3D planning unit (Nucletron Plato) HDR unit (Nucletron)</p> <p>Dose/frequency/details: Total Rx length: 4–8 cm Total Rx time: 10–16 min. Brachytherapy delivered at weeks 1, 2 and 3 at 7.5 Gy per fraction or at weeks 1 and 2 at 10 Gy per fraction. In poor performance status patient's two fractions were preferred.</p> <p>Technical details: Bronchoscopy under local anesthesia, used opaque dummy wire for fluoroscopic verification</p> <p>Treatment Intention: Palliative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> All patients eval at 6th wk and at the 3rd month of Rx Speiser's scoring index for scoring endobronchial obstruction Performance status - ECOG scale |
| Celikoglu-2006, #606 | <p>Study Objective: To study the effectiveness, safety, and feasibility of initial debulking by intratumoral chemotherapy with cisplatin followed by irradiation in the treatment of obstructive inoperable NSCLC.</p> <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): % obstruction, mean survival</p> | <p>Intervention name: Intratumoral cisplatin followed by radiation</p> <p>Vendor name: Not reported</p> <p>Dose/frequency/details: Intratumoral chemotherapy was performed under LA through a flexible fiber optic bronchoscope Chemotherapy: Injection of up to 40 mg cisplatin (approx. 2 mg cisplatin per cubic centimeter of the tumor) at each Rx session. Cisplatin given every week, for 3 weeks (on days 1, 8, 15 and 22).</p> |

| Study | Study Outcomes | Interventions |
|----------------------------|---|---|
| | <p>Cause of death: Not reported</p> <p>Length of FU: Not reported</p> | <p>Radiation: At 3-7 days after the last session of intratumoral chemotherapy 60 Gy in 24 fractions (2.5 Gy per fraction)</p> <p>Technical details: None</p> <p>Treatment Intention: Curative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • In the absence of a bronchial residual tumor 1 month after irradiation, the patient's condition was assessed at 3-monthly intervals by clinical findings, chest X-ray film, and bronchoscopy. • Survival period was measured from the first intratumoral session day. • Criteria for efficacy of debulking: <ul style="list-style-type: none"> Good response: >50% ↑ in diameter of the airway's lumen Moderate response: 25—50% ↑ in diameter of the lumen Small response: <25% ↑ in diameter of the lumen |
| <p>Chhaged-2006, #696</p> | <p>Study Objective: In patients with advanced NSCLC treated with chemotherapy, we compared survival in patients with treated central airway obstruction to those who did not have central airway obstruction.</p> <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): Survival, toxicity</p> <p>Cause of death: Not reported</p> <p>Length of FU: Not reported</p> | <p>Intervention name: Therapeutic bronchoscopy (laser and/or stent insertion) Patients received chemotherapy (with or without external beam radiation) prior or after or both time periods after therapeutic bronchoscopy (laser and/or stent insertion)</p> <p>Vendor name: Rigid bronchoscopy (Efer-Dumon; Karl Storz Optics; Tuttlingen, Germany) Laser ablation (Smart 1064 DW; Deka Medical Electronic Associates; Calenzano, Italy)</p> <p>Dose/frequency/details: NA</p> <p>Technical details: Rigid bronchoscopy under general anesthesia Laser ablation using either rigid or flexible bronchoscope</p> <p>Treatment Intention: Not clearly stated</p> <p>Follow-up and Evaluation Criteria: Survival calculated from the date of administration of chemotherapy or therapeutic bronchoscopy, whichever was earlier.</p> |
| <p>Guilcher-2011, #188</p> | <p>Study Objective: To assess retrospectively the efficacy and tolerance of HDR brachytherapy alone in the Rx of patients with</p> | <p>Intervention name: HDR-brachytherapy</p> |

| Study | Study Outcomes | Interventions |
|---------------------------|---|---|
| | <p>endobronchial tumors that cannot be removed surgically or benefit from EBRT</p> <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): OS, CSS, Local Control, Toxicity</p> <p>Cause of death: Total dead: 128 (57%) LC: 57 (45%) Intercurrent disease: 45 (35%) Rx toxicity: 13 (10%) Other cancers: 12(9%) Unknown cause: 1 (1%)</p> <p>Length of FU: 30.4 months (9-116) (note this is mean with range)</p> | <p>Vendor name: Not reported</p> <p>Dose/frequency/details: Total dose: <30 Gy: 160 (71%); ≥30 Gy: 66 (29%) Fractions: ≤5: 106 (47%); > 5: 120 (53%) Dose/fraction: ≤5: 148 (65%); > 5: 78 (35%)</p> <p>Technical details: Tumor located by bronchoscopy. ≥ 1 catheters were implanted next to the lesion via the working channel of the bronchoscope. Target volume was drawn with a 1-to 2-cm safety margin. The dose was prescribed to be delivered at 1 cm from an Iridium-192 source.</p> <p>Treatment Intention: Not reported</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • FU varied according to the center but usually included bronchoscopy and chest CT scan every 6 months. • Speiser and Spratling scale to assess radiation bronchitis |
| <p>Jimenez-1999, #978</p> | <p>Study Objective: To conduct a prospective RCT in order to assess the effectiveness and safety of photodynamic therapy versus laser resection in 31 patients with partial or complete tracheobronchial obstruction due to inoperable NSCLC.</p> <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): Survival, toxicity, response rate, time to Rx failure</p> <p>Cause of death: Total dead: 23 (74.2%) Progression of malignancy PHDT: 7 (50%) YAGL: 12 (71%) Probably related to Rx: PHDT: 1 (7%) YAGL: 0</p> | <p>Intervention name: PHDT YAGL</p> <p>Vendor name: Photofrin; Lederle, Vancouver, Canada</p> <p>Dose/frequency/details: PHDT: Tumors were irradiated (630-nm light) via a flexible fiberoptic bronchoscope 40-50 h after IV 2 mg/kg DHE. 2nd irradiation done if parts of tumor failed to show signs of necrosis 96-120 h after 1st irradiation. Max of 3 doses of DHE at 1-month intervals and up to 6 laser photoradiations, with max of 2 photoradiations/ session. YAGL: Rigid bronchoscope, general anesthesia, performed using 15-80 W pulses and a pulse duration of 0.5-1.5 s. Sessions repeated every 2-4 days until it was considered that further application would not give additional benefits.</p> <p>Technical details: None</p> |

| Study | Study Outcomes | Interventions |
|-------------------------------|---|--|
| | <p>Death from hemoptysis and presumed progression of the disease PHDT: 1 (7%) YAGL: 1 (6%) Unknown reasons: 3 (10%)</p> <p>Length of FU: Protocol specified all patients to be followed for 24 months.</p> | <p>Treatment Intention: Palliation</p> <p>Follow-up and Evaluation Criteria: Control bronchoscopy after either PDT or Nd-YAG laser resection was performed 1 week after PDT, every month for 3 months and at 6 and 12 months (and at 18 months, if possible) thereafter. A</p> |
| <p>Jones-2001, #1862</p> | <p>Study Objective: To summarize early experience with PHDT in the palliation of symptoms in patients with terminal lung cancer and obstructing endobronchial lesions.</p> <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): Survival, symptoms</p> <p>Cause of death: Not reported</p> <p>Length of FU: Not reported</p> | <p>Intervention name: PHDT</p> <p>Vendor name: Coherent Lambda plus Argon Laser (Santa Clara, CA)</p> <p>Dose/frequency/details: Porfirmer sodium (2.0 mg/kg) given 48 hours prior to laser, 630 nm wavelength, average light delivered per session (200 J/cm)</p> <p>Technical details: Flexible bronchoscope was used</p> <p>Treatment Intention: Palliation</p> <p>Follow-up and Evaluation Criteria: Not reported</p> |
| <p>Langendjik-2001, #2144</p> | <p>Study Objective: To test the hypothesis that the addition of endobronchial BCHY to EBRT provides higher levels of palliation of dyspnea and other respiratory symptoms and improvement of QOL in patients with NSCLC with endobronchial tumor</p> <p>Primary outcome: Response rate of dyspnea Definition: Response was defined as</p> <ul style="list-style-type: none"> • Baseline score 'moderate or severe', with improvement to 'mild' or 'nil' on at least 2 consecutive assessments in the first 3 months after the end of RT=improvement • Baseline score 'mild', with improvement to 'nil' on at least 2 consecutive assessments in the first 3 months after the end of RT= improvement • Baseline score 'mild', with 'mild' on at least 2 consecutive assessments in the first 3 months after the end of RT= control • Baseline score 'nil', with 'nil' on at least 2 consecutive assessments in the first 3 months after the end of RT = prevention | <p>Intervention name: BCHY</p> <p>Vendor name: For BCHY: HDR-microselectron (Nucletron, Leersum, The Netherlands)</p> <p>Dose/frequency/details: Palliative schedule: 3 Gy/fraction (4 times a week) up to a total dose of 30 Gy (100%) without correction for lung tissue density. Radical schedule: 2.25 Gy/fraction (4 times a week) to a total dose of 45 Gy followed by a boost up to 60 Gy using fraction doses of 2.5 Gy (four times a week). Correction was made for lung tissue density (0.3). BCHY: Under LA, Iridium 1⁹² stepping source, using a stepping size of 2.5 or 5 mm Palliative: 23% (11 of 48) in EBRT; 19% (9 of 47) in EBRT+BCHY Radical: 77% (37 of 48) in EBRT; 81% (38 of 47) in EBRT+BCHY</p> <p>Technical details: Note that both palliative & radical RT based on severity of disease and</p> |

| Study | Study Outcomes | Interventions |
|----------------------|---|---|
| | <p>Secondary outcome(s): Re-expansion of atelectasis, survival and complications</p> <p>Definitions: Not reported</p> <p>List of Outcome(s): QOL and other respiratory symptoms were evaluated on exploratory basis</p> <p>Cause of death: EBRT +BCHY: Total: 44/48 (92%) Local progression: 12 (26%) Massive hemoptysis: 7 (15%) Mets: 16 (34%) Local progression + mets: 1 (2%) Intercurrent disease: 1 (2%) Unknown: 6(13%)</p> <p>EBRT: Total: 40/47 (85%) Local progression: 17 (35%) Massive hemoptysis: 6 (13%) Mets: 11(23%) Local progression + mets: 2 (4%) Intercurrent disease: 4 (8%) Unknown: 1(2%)</p> <p>Length of FU: Not reported</p> | <p>performance status was given to both Rx arms.</p> <p>Treatment Intention:</p> <ul style="list-style-type: none"> Note that both palliative & radical RT based on severity of disease and performance status was given to both Rx arms. Palliative RT: Patients with WHO performance status 3, supraclavicular lymph node mets and/or distant mets with symptoms related to intrathoracic tumor Radical RT: Patients with stage I or II disease with a tumor diameter > 4 cm or stage IIIa and stage IIIb disease without supraclavicular lymph node mets and a WHO performance \leq 2 <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> QOL and RS were assessed before the start of RT and subsequently 2 weeks, 6 weeks and 3, 6 and 12 months after end of RT Dutch version of the EORTC QLQ-C30 (version 1.0) and the lung cancer module QLQ-LC13 were used to measure QOL |
| Lencioni-2008, #2238 | <p>Study Objective: To assess the feasibility, safety, & effectiveness of percutaneous CT-guided RFA in the Rx of NSCLC & pulmonary mets.</p> <p>Primary outcome: Technical success, safety (Rx-related complications & changes in pulmonary function), and confirmed CR of the target tumors</p> <p>Definition: Technical success defined as correct placement of the ablation device into all target tumors with completion of the planned ablation protocol—i.e., maintenance of the target temperature of 90°C for the required time according to tumor size. Treatment-related complications were those occurring within 30 days from treatment. Complications were assessed on a per-procedure basis and defined as follows. Minor: Those resulting in no sequel or needing nominal treatment or a short hospital stay for observation. Major: Those resulting in readmission to the hospital for Rx, an unplanned increase in the level of care, extended</p> | <p>Intervention name: RFA</p> <p>Vendor name: RITA Medical Systems Model 1500 and Model 1500X (AngioDynamics, Queensbury, NY)</p> <p>Dose/frequency/details: Time spent achieving target temperature of 90 degree Celsius.</p> <p>Technical details: Not reported</p> <p>Treatment Intention: Not reported</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> OS: Time from the beginning of Rx to last FU visit or death from any cause was used. CSS: Time from the beginning of Rx to last FU visit or cancer related death was used. FU visits scheduled 1 & 3 months after Rx & then at 3-months intervals for up to 2 years. |

| Study | Study Outcomes | Interventions |
|----------------------|--|---|
| | <p>hospitalization, permanent adverse sequel, or death.</p> <p>Secondary outcome(s): OS, CSS, QOL Definitions: Not reported</p> <p>List of Outcome(s): NA</p> <p>Cause of death: Reported but cannot be discerned</p> <p>Length of FU: Mean 15 months (1-30)</p> | <ul style="list-style-type: none"> Physical examination; radiological imaging for tumor assessment, including CT, KPS, PFT, FACT-L, SF-12, adverse events. |
| Moghissi-1999, #2591 | <p>Study Objective: To compare the efficacy and adverse effects of the two Rx in terms of palliation of breathlessness, cough, hemoptysis, chest pain, stridor, resp function, performance status, QOL, days of inpatient management and survival.</p> <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): Survival, Obstructive symptoms, PS</p> <p>Cause of death: Not reported</p> <p>Length of FU: NA</p> | <p>Intervention name: EBRT EBHT (Brachytherapy, Cryotherapy, Laser)</p> <p>Vendor name: Not reported</p> <p>Dose/frequency/details: EBRT: 17 Gy in 2 fractions (n=12) EBHT: 13 Gy (n=13)</p> <p>Technical details: Not reported</p> <p>Treatment Intention: Palliative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> Patients assessed before Rx, at time of randomization, then 4 weeks, 2, 4 & 6 months thereafter QOL: Rotterdam Symptoms checklist and patient diary |
| Muto-2000, #2665 | <p>Study Objective: To demonstrate that a fractionated HDR BCHY is tolerable for patients with advanced NSCLC and improves symptoms</p> <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): Survival, toxicity</p> | <p>Intervention name: EBRT HDR BCHY</p> <p>Vendor name: Not reported</p> <p>Dose/frequency/details: EBRT: 15 MV linear accelerator, daily dose 2 Gy, delivered 60 Gy to tumor bed and 50 Gy to mediastinum. BCHY (10 Gy): 10 GY in single fraction BCHY (14Gy) + EBRT: 14 Gy (2 fractions of 7 Gy)</p> |

| Study | Study Outcomes | Interventions |
|----------------------------|---|--|
| | <p>Cause of death: Not reported</p> <p>Length of FU: 5-36 months</p> | <p>BCHY (15Gy, 1cm) + EBRT: 15 Gy (3 fractions of 5Gy each) (1 cm from central axis)</p> <p>BCHY (15Gy, 0.5 cm) + EBRT: 15 Gy (3 fractions of 5Gy each) (0.5 cm from central axis)</p> <p>Technical details: None</p> <p>Treatment Intention: Palliative</p> <p>Follow-up and Evaluation Criteria: Chest x-ray after 1-3 months from last HDR BCHY Bronchoscopy & CT scan after 6 months</p> |
| <p>Mallick-2006, #2417</p> | <p>Study Objective: To compare the subjective and objective responses to 3 Rxs for endobronchial palliation, response duration, QOL and complications in stage III NSCLC.</p> <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): Symptom and obstruction score, duration of symptoms, QOL, complications</p> <p>Cause of death: Not reported</p> <p>Length of FU: 6 months (2-17)</p> | <p>Intervention name: Brachytherapy External beam radiation</p> <p>Vendor name: BCHY (Treatment planning done with Nucletron PLATO treatment)</p> <p>Dose/frequency/details:</p> <ol style="list-style-type: none"> i. EBRT-30 Gy in 10 fractions+ BCHY-16Gy in 2 fractions; ii. EBRT-30 Gy in 10 fractions+ BCHY-10Gy single fraction; iii. BCHY-15Gy single fraction <p>Technical details: EBRT: Megavoltage photon beam of Co⁶⁰ or a 6-MV linear accelerator</p> <p>Treatment Intention: Palliative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Symptoms were scored before Rx and at monthly intervals after Rx completion. Chest X-ray was done at monthly intervals. QOL assessments (EORTC QLQ-C30 and LC 13 version) were done before and at end of 1 months after Rx. • Speiser Score for Symptom and Obstruction • Toxicity: RTOG morbidity scoring criteria |
| <p>Petera-2001, #2914</p> | <p>Study Objective: To report the effect of combination therapy (teletherapy + brachytherapy) given as curative & palliative on symptomatic response, tumor response, survival rate and complications (paraphrased)</p> | <p>Intervention name: Teletherapy + BCHY</p> <p>Vendor name: HDR loading system (Gammamed, MDS, Nordion, Hahn, Germany)</p> |

| Study | Study Outcomes | Interventions |
|-------------------|---|--|
| | <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): Survival, symptoms</p> <p>Cause of death: Not reported</p> <p>Length of FU: Median FU of living patients: BCHY (Cur): 304 days (92-638) BCHY (Pall): 274 days (212-881) Calculated from the first BCHY Rx.</p> | <p>Dose/frequency/details: BCHY (Cur): BCHY dose was 3X5 Gy, teletherapy dose was 50 Gy in 25 fractions to the mediastinum and 60Gy in 30 fractions to the primary tumor. BCHY (Pall): BCHY dose was 3X7.5 Gy, mean dose from EBRT was 42.3 Gy (10-56).</p> <p>Technical details: None</p> <p>Treatment Intention: Curative and palliative</p> <p>Follow-up and Evaluation Criteria: Symptom evaluation: Scoring system by Speiser & Spralling Bronchoscopy & chest X-ray 6 weeks after compulsion of RT.</p> |
| Stout-2000, #3640 | <p>Study Objective: To evaluate the clinical and QOL of patients receiving BCHY and EBRT as a primary palliative Rx in advanced lung cancer.</p> <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): Symptoms (clinician & patient assessment), survival, QOL (Hospital Anxiety and Depression Scale)</p> <p>Cause of death: Not reported</p> <p>Length of FU: Not reported. Patients followed up till dead.</p> | <p>Intervention name: BCHY EBRT</p> <p>Vendor name: BCHY: HDR-microselectron</p> <p>Dose/frequency/details: BCHY: 15 Gy dose, flexible bronchoscope EBRT: 8 exposures over 10-12 days- max s/c dose of 30Gy</p> <p>Technical details: None</p> <p>Treatment Intention: Palliative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> • Positive symptom: If symptom absent at baseline and absent at follow-up assessment OR if symptom is graded mild at baseline and graded mild OR absent at follow-up assessment OR if symptom is graded moderate or severe at baseline and graded mild or absent at follow-up assessment. • Global palliation: Each negative symptom endpoint was assigned a score of 0 and a positive endpoint 1, giving a range of scores 0 to 9. A total score of 0 to 4 was poor palliation and 5 to 9 good palliation. • Baseline & 4, 8, 16, 26, 38 and 52 weeks and every 3 months afterwards. • Acute Rx side effects: those that occurred within 4-8 weeks of Rx. <p>Intervention name:</p> |
| van Boxem- | <p>Study Objective: To evaluate the cost-effectiveness of YAGL and</p> | <p>Intervention name:</p> |

| Study | Study Outcomes | Interventions |
|-----------------------|--|---|
| 1999, #427 | <p>ECAU for palliation in patients with symptomatic endoluminal obstruction due to NSCLC</p> <p>Primary outcome: Not reported</p> <p>Definition: NA</p> <p>Secondary outcome(s): Not reported</p> <p>Definitions: NA</p> <p>List of Outcome(s): Improvement of symptoms, complication rate, mean survival</p> <p>Cause of death: Not reported</p> <p>Length of FU: Not reported</p> | <p>YAGL ECAU</p> <p>Vendor name: YAGL: Sharplan Lasers, Allendale, NJ ECAU: Valleylab; Boulder, CO</p> <p>Dose/frequency/details: Coagulation with both interventions was performed using power settings up to 55 W YAGL: 1.1 ±0.3 session per patient ECAU: 1.2 ±0.4 session per patient</p> <p>Technical details: Flexible and rigid bronchoscopes were used in most cases.</p> <p>Treatment Intention: YAGL: Palliative ECAU: Palliative</p> <p>Follow-up and Evaluation Criteria:</p> <ul style="list-style-type: none"> Planned FU times Not reported Calculated from time after therapy ends <p>Note: Dyspnea improvement was evaluated as yes or no by 2 authors</p> |
| Vucicevic-1999, #4010 | <p>Study Objective: To assess the results of HDR BCHY in combination with EBRT in NSCLC patients</p> <p>Primary outcome: Not reported</p> <p>Definition: NA</p> <p>Secondary outcome(s): Not reported</p> <p>Definitions: NA</p> <p>List of Outcome(s): Survival, symptoms, toxicity</p> <p>Cause of death: Not reported</p> <p>Length of FU: Average FU: 7 months (2-19)</p> | <p>Intervention name: EBRT plus HDR BCHY</p> <p>Vendor name: Not reported</p> <p>Dose/frequency/details: HDR BCHY: Mean dose of 2100 cGy in 3 fractions (1 fraction per week) EBRT: High energy photo beam (6 or 10 MV) up to a total dose of 3000-4500 cGY in 10-22 fractions/ 5 fractions per week.</p> <p>Technical details: None</p> <p>Treatment Intention: Palliative</p> <p>Follow-up and Evaluation Criteria: Bronchoscopy & chest X-ray 1-3 months after BCHY Rx. OS was calculated by Kaplan Meier from the time of completion</p> |

| Study | Study Outcomes | Interventions |
|----------------------|---|--|
| Weinberg-2010, #4066 | <p>Study Objective: To review the outcomes of combined PHDT + HDR-BCHY for patients with symptomatic obstruction from endobronchial NSCLC</p> <p>Primary outcome: Not reported Definition: NA</p> <p>Secondary outcome(s): Not reported Definitions: NA</p> <p>List of Outcome(s): Survival, toxicity</p> <p>Cause of death: Not reported</p> <p>Length of FU: Not reported</p> | <p>Intervention name: HDR-BCHY Chemotherapy PHDT</p> <p>Vendor name: Not reported</p> <p>Dose/frequency/details: BCHY: Flexible bronchoscope, 500 Gy delivered to 0.5cm depth via a nucletron remote after loading HDR unit. 2 additional HDR Rx delivered at weekly intervals for a total dose of 15 Gy in 3 fractions. PHDT: 2 mg/kg photoforin 48 hrs prior to given Rx. 630 nm light to a dose of 200 J/cm²</p> <p>Technical details: None</p> <p>Treatment Intention: Palliative</p> <p>Follow-up and Evaluation Criteria: All patients had a routine monthly bronchoscopy for first 3 months and then every 3-6 months as indicated</p> |

Appendix Table C15. Survival and local control outcomes of studies that address Key Question 3

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|-----------------------|--|---|---|--|------------|
| Allison-2004, #108 | Overall survival: 10.3 months (± 4.1) (calculated) Cancer/disease specific survival: Not reported | Overall survival: NA Cancer/disease specific survival: NA | Local control: 100 %. No patient had local recurrence till they all died. However, mean or median FU time not reported. | Local control: NA | No |
| Chella-2000, #654 | YAGL + BCHY Overall survival: Median survival: 10.3 months (method Not reported) Cancer/disease specific survival: Not reported | YAGL Overall survival: Median survival: 7.4 months (method Not reported) Cancer/disease specific survival: Not reported | YAGL + BCHY Local control: Not reported | YAGL Local control: Not reported | No |
| Celebioglu-2002, #604 | Overall survival: Not reported Cancer/disease specific survival: Not reported | Overall survival: NA Cancer/disease specific survival: NA | Local control: Not reported | Local control: NA | No |
| Celikoglu-2006, #606 | Overall survival: Not reported Cancer/disease specific survival: Not reported | Overall survival: NA Cancer/disease specific survival: NA | Local control: Not reported | Local control: Not reported | No |
| Chhajed-2006, #696 | STNT or LASR: Overall survival: Median survival : 8.4 months (4.8-17.1), 3-months survival: 90% 6-months survival: 71% 12-months survival: 40% Cancer/disease specific survival: Not reported | Overall survival: NA Cancer/disease specific survival: NA | Local control: 9 patients had tumor growth. Thus local control was 87% (at unspecified time, assumption at the time of study closeout, average FU period not given) | Local control: NA | Yes |
| Guilcher-2011, #188 | Overall survival: Median survival: 28.6 months 2 yr: 57% 5 yr: 29% Cancer/disease specific survival: 2 yr: 81% 5 yr: 56% | Overall survival: NA Cancer/disease specific survival: NA | Local control: G3data | Local control: NA | No |

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|-------------------------|--|--|--|--|------------|
| Jimenez-1999, #978 | PHDT: Overall survival: Median survival: 265 days Cancer/disease specific survival: Not reported | YAGL: Overall survival: Median survival 95 days (p=0.007) Cancer/disease specific survival: Not reported | PHDT: Local control: Not reported | YAGL: Local control: Not reported | No |
| Jones-2001, #1862 | Overall survival: Mean survival: From diagnosis: 10.5 months Post PHDT Rx: 5.5 months Cancer/disease specific survival: Not reported | Overall survival: NA Cancer/disease specific survival: NA | Local control: Not reported | Local control: NA | No |
| Langendjik-2001, #2144 | EBRT +BCHY: Overall survival: Median survival: 7.0 months (95%CI: 5.3 to 8.9) Cancer/disease specific survival: Not reported | EBRT: Overall survival: Median survival: 8.5 months (95%CI: 5.4 to 11.6) Cancer/disease specific survival: Not reported | EBRT +BCHY: Local control: Not reported | EBRT: Local control: Not reported | No |
| Lencioni-2008, #2238 | Overall survival: 1 yr: 70% (95% CI: 51 to 83) 2 yr: 48% (95% CI: 30 to 65) Cancer/disease specific survival: 1 yr: 92% (95% CI: 78–98) 2 yr: 73% (95% CI: 54–86) | Overall survival: NA Cancer/disease specific survival: NA | Local control: Not reported | Local control: NA | Yes |
| Moghissi-1999, #2591 | EBRT: Overall survival: Median survival: 182 days 1 yr survival: 26% Cancer/disease specific survival: Not reported | EBHT: Overall survival: Median survival: 150 days 1 yr survival: 29% Cancer/disease specific survival: Not reported | Local control: Not reported | Local control: Not reported | No |
| Muto-2000, Italy, #2665 | Overall survival: Mean survival from diagnosis: 11.1 months Mean survival from last HDR BCHY Rx: 9.7 months Cancer/disease specific survival: Not reported | Overall survival: NA Cancer/disease specific survival: NA | Local control: Not reported | Local control: NA | No |
| Mallick-2006, #2417 | Overall survival: Not reported Cancer/disease specific survival: Not reported | Overall survival: Not reported Cancer/disease specific survival: Not reported | Local control: Not reported | Local control: Not reported | No |
| Petera-2001, #2914 | Overall survival: Median survival (from diagnosis) | Overall survival: NA | Local control: Not reported | Local control: NA | Yes |

| Study | Survival Outcomes for Intervention Group 1 | Survival Outcomes for Intervention Group 2 | Local Control Outcomes for Intervention Group 1 | Local Control Outcomes for Intervention Group 2 | Arm |
|-----------------------|--|---|---|---|-----|
| | BCHY (Cur): 365 days (92-670) BCHY (Pall): 242 days (30-881) Median survival (1 st BCHY Rx) BCHY (Cur): 245 days (1-396) BCHY (Pall): 242 days (1-850) Cancer/disease specific survival: Not reported | Cancer/disease specific survival: Not reported | | | |
| Stout-2000, #3640 | BCHY: Overall survival: Median: 250 days 1 yr: 22% 2 yr: 2% Cancer/disease specific survival: Not reported | EBRT: Overall survival: Median: 287 days (p=0.042) 1 yr: 38% 2 yr: 10% Cancer/disease specific survival: Not reported | Local control: Not reported | Local control: Not reported | No |
| van Boxem-1999, #427 | Overall survival: YAGL: 8.0 ± 2.5 m Cancer/disease specific survival: Not reported | Overall survival: ECAU: 11.5 ± 3.5 m Cancer/disease specific survival: Not reported | Local control: Not reported | Local control: Not reported | No |
| Vucicevic-1999, #4010 | Overall survival: G3 data Fig 5 page 380 Cancer/disease specific survival: Not reported | Overall survival: NA Cancer/disease specific survival: NA | Local control: Not reported | Local control: NA | No |
| Weinberg-2010, #4066 | Overall survival: Consult TR Page 54 table 2 Cancer/disease specific survival: Not reported | Overall survival: NA Cancer/disease specific survival: NA | Local control: Not reported | Local control: NA | No |

Appendix Table C16. Miscellaneous outcomes of studies that address Key Question 3

| Study | Intervention Group 1 | Intervention Group 2 |
|-----------------------|---|--|
| Allison-2004, #108 | <p>Lung function: Not reported</p> <p>Obstructive symptoms: Not reported</p> <p>Quality of life: Not reported</p> <p>Performance status: Not reported Baseline KPS: 45 (\pm7.1) Post Rx KPS: 77 (\pm9.5) Diff: $p < 0.001$ using Wilcoxon rank sum</p> <p>Others: Not reported</p> | <p>Lung function: NA</p> <p>Obstructive symptoms: NA</p> <p>Quality of life: NA</p> <p>Performance status: NA</p> <p>Others: NA</p> |
| Chella-2000, #654 | <p>YAGL + BCHY</p> <p>Lung function: FEV₁ (L): Pre: 1.43 (\pm0.6) Post: 2.32 (\pm0.4) FEV₁ (%): Pre: 53.2 (\pm11.2) Post: 65.4 (\pm12.1)</p> <p>Obstructive symptoms: Speiser's index: Pre: 6.9 (\pm0.7) Post: 2.7 (\pm0.9)</p> <p>Quality of life: Not reported</p> <p>Performance status: Not reported</p> <p>Others: Not reported</p> | <p>YAGL</p> <p>Lung function: FEV₁ (L): Pre: 1.35 (\pm0.7) Post: 2.16 (\pm0.6) FEV₁ (%): Pre: 52.4 (\pm10.7) Post: 63.4 (\pm12.3)</p> <p>Obstructive symptoms: Speiser's index: Pre: 6.4 (\pm0.7) Post: 3.0 (\pm0.8)</p> <p>Quality of life: Not reported</p> <p>Performance status: Not reported</p> <p>Others: Not reported</p> |
| Celebioglu-2002, #604 | <p>Lung function: Not reported</p> <p>Obstructive symptoms: BCHY Dyspnea: Pre: 2 Post: 0 (< 0.05) Cough: Pre: 2 Post: 1 (< 0.05) Hemoptysis: Pre: 2 Post: 1 (< 0.05) Pneumonitis: Pre: 2 Post: 1 (< 0.05) BOI:</p> | <p>Lung function: NA</p> <p>Obstructive symptoms: NA</p> |

| Study | Intervention Group 1 | Intervention Group 2 |
|-------------------------|--|---|
| | Pre: 6 Post: 4 (<0.05) | |
| | Quality of life: NA | Quality of life: NA |
| | Performance status: NA | Performance status: NA |
| | Others: NA | Others: NA |
| Celikoglu-2006, #606 | Lung function: Not reported | Lung function: NA |
| | Obstructive symptoms: Reported as % obstruction without any detail Pre Rx: 86.8 %±15.2 (for 28 obstructive sites) Post Rx: 36.0 %± 31.1 (for 28 obstructive sites) | Obstructive symptoms: NA |
| | Obstruction improvement Good: 11 (48%) Moderate: 8 (35%) Small: 4(17%) | Quality of life: NA |
| | Quality of life: Not reported | Performance status: NA |
| | Performance status: Not reported | Others: NA |
| | Others: Not reported | |
| Chhajed-2006, #696 | Lung function: Not reported | Lung function: NA |
| | Obstructive symptoms: Not reported | Obstructive symptoms: NA |
| | Quality of life: Not reported | Quality of life: NA |
| | Performance status: Not reported | Performance status: NA |
| | Others: Not reported | Others: NA |
| Guilcher-2011, #188 | Lung function: Not reported | Lung function: NA |
| | Obstructive symptoms: Not reported | Obstructive symptoms: NA |
| | Quality of life: Not reported | Quality of life: NA |
| | Performance status: Not reported | Performance status: NA |
| | Others: Not reported | Others: NA |
| Jimenez-1999, #978 | Lung function: Not reported | Lung function: Not reported |
| | Obstructive symptoms: Amelioration of symptoms was similar in both the groups. Quantitative data not reported. | Obstructive symptoms: Amelioration of symptoms was similar in both the groups. Quantitative data not reported. |
| | Quality of life: Not reported | Quality of life: Not reported |

| Study | Intervention Group 1 | Intervention Group 2 |
|------------------------|--|--|
| | Performance status: Not reported | Performance status: Not reported |
| | Others: Not reported | Others: Not reported |
| Jones-2001, #1862 | Lung function: Not reported | Lung function: NA |
| | Obstructive symptoms: Not reported | Obstructive symptoms: NA |
| | Quality of life: Not reported | Quality of life: NA |
| | Performance status: Not reported | Performance status: NA |
| | Others: Improvement I in subjective symptoms of obstruction: 9 (90%) Acute hemoptysis resolved: 7 (70%) | Others: NA |
| Langendjik-2001, #2144 | Lung function: NA | Lung function: NA |
| | Obstructive symptoms: EBRT +BCHY: % Response Dyspnea: 18/39 (46%) Cough: 24% Hemoptysis: 86% Chest pain: 80% Pain in arm/shoulder: 74% | Obstructive symptoms: EBRT: % Response Dyspnea: 16/43 (37%) (p=0.29) Cough: 38% (NSS) Hemoptysis: 82% (NSS) Chest pain: 67% (NSS) Pain in arm/shoulder: 69% (NSS) (Note: numerator and denominator unknown and not advisable to calculate as patients may have been omitted and assumptions may give false results) |
| | Dyspnea symptom score (all patients): 2 wks: -5.4 6 wks: -3.9 3 months: 5.7 6 months: 15.0 12 months: 2.2 | Dyspnea symptom score (all patients): 2 wks: 7.4 (Δ -12.9) 6 wks: 8.9 (Δ -12.8) (p=0.02) (note: unclear about p value) 3 months: 10.8 (Δ -5.1) 6 months: 10.6 (Δ 4.3) 12 months: 15.2 (Δ -13.0) |
| | Dyspnea symptom score (patients with tumor in main bronchus): 2 wks: -22.6 6 wks: -10.8 3 months: -6.8 | Dyspnea symptom score (patients with tumor in main bronchus): 2 wks: 12.4 (Δ -35.0) 6 wks: 17.8 (Δ -28.6) 3 months: 24.8 (Δ -31.6) |
| | Quality of life: Not reported | Quality of life: Not reported |
| | Performance status: Not reported | Performance status: Not reported |

| Study | Intervention Group 1 | Intervention Group 2 |
|-------------------------|--|---|
| Lencioni-2008, #2238 | Others: None Lung function: (n=22) FEV, L | Others: None Lung function: NA |
| | 0 months: 1.9 (± 0.9) 1 months: 1.7 (± 1.1) 3 months: 1.7 (± 0.9) 6 months: 1.6 (± 0.9) 12 months: 1.5 (± 0.7) FEV, % predicted 0 months: 68.8 (± 26.9) 1 months: 65.3 (± 24.6) 3 months: 71.0 (± 27.2) 6 months: 62.5 (± 18.5) 12 months: 63.4 (± 20.7) | Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: NA |
| | Obstructive symptoms: Not reported | |
| | Quality of life: FACT-G 0 months: 80.5 (± 11.2) 12 months: 82.2 (± 11.1) LCS 0 months: 22.5 (± 3.9) 12 months: 23.6 (± 3.1) TOI 0 months: 64.2 (± 10.6) 12 months: 67.5 (± 8.0) PCS 0 months: 44.4 (± 10.8) 12 months: 46.0 (± 10.2) MCS 0 months: 47.6 (± 9.6) 12 months: 49.6 (± 10.3) | |
| | Performance status: Not reported | |
| | Others: None | |
| Moghissi-1999, #2591 | EBRT: Lung function: Relief of breathlessness: 32% | EBHT: Lung function: Relief of breathlessness: 28% |
| | Obstructive symptoms: Not reported | Obstructive symptoms: Not reported |
| | Quality of life: Not reported | Quality of life: Not reported |
| | Performance status: | Performance status: |

| Study | Intervention Group 1 | Intervention Group 2 |
|----------------------------|---|--|
| Muto-2000, Italy, #2665 | WHO PS: 14% Others: Palliation of major thoracic symptoms: 27% | WHO PS: 38% (difference 24%; 95%CI: 8 to 56) Others: Palliation of major thoracic symptoms: 22% |
| | Lung function: Not reported Obstructive symptoms: Dyspnea: BCHY (10 Gy): Pre: 90 % Post: 20 % BCHY (14Gy) + EBRT: Pre: 87 % Post: 15% BCHY (15Gy, 1cm) + EBRT: Pre: 88 % Post: 10 % BCHY (15Gy, 0.5 cm) + EBRT: Pre: 85 % Post: 5 % Cough: BCHY (10 Gy): Pre: 92 % Post: 42 % BCHY (14Gy) + EBRT: Pre: 96 % Post: 28 % BCHY (15Gy, 1cm) + EBRT: Pre: 90 % Post: 12 % BCHY (15Gy, 0.5 cm) + EBRT: Pre: 91 % Post: 11 % Hemoptysis: BCHY (10 Gy): Pre: 10 % Post: 0 % BCHY (14Gy) + EBRT: Pre: 7 % Post: 1 % BCHY (15Gy, 1cm) + EBRT: Pre: 8 % Post: 1 % BCHY (15Gy, 0.5 cm) + EBRT: Pre: 12 % Post: 0 % | Lung function: NA Obstructive symptoms: NA |
| | Quality of life: | Quality of life: |

| Study | Intervention Group 1 | Intervention Group 2 |
|------------------------|---|---|
| | Not reported | NA |
| | Performance status: Not reported | Performance status: NA |
| | Others: None | Others: NA |
| Mallick-2006, #2417 | Lung function: Not reported | Lung function: Not reported |
| | Obstructive symptoms: Obstructive pneumonia (% incidence) EBRT+BCHY-16Gy: Pre: 9 (60%) Post: 9 (100%) (NSS) EBRT+BCHY-10Gy: Pre: 10 (67%) Post: 7 (70%) (NSS) Obstructive pneumonia (median time to relapse in months) EBRT+BCHY-16Gy: 4 EBRT+BCHY-10Gy: 5 Obstructive pneumonia (median time to progression in months) EBRT+BCHY-16Gy: 7 EBRT+BCHY-10Gy: 7 | Obstructive symptoms: Obstructive pneumonia (% incidence) BCHY-15Gy: Pre: 10 (67) Post: 8 (80) (NSS) Obstructive pneumonia (median time to relapse in months) BCHY-15Gy: 6 (NSS) Obstructive pneumonia (median time to progression in months) BCHY-15Gy: 6 (NSS) |
| | Quality of life: QLQ-C3 (Global Health status): EBRT+BCHY-16Gy: Pre: 37 Post: 75 (↑103%) EBRT+BCHY-10Gy: Pre: 35 Post: 63 (↑80%) QLQ-C3 (Physical Functioning): EBRT+BCHY-16Gy: Pre: 71 Post: 90 (↑27%) EBRT+BCHY-10Gy: Pre: 74 Post: 85 (↑15%) QLQ-LC13 (Symptom Scale: Dyspnea) EBRT+BCHY-16Gy: Pre: 33 Post: 4 (↓88%) EBRT+BCHY-10Gy: Pre: 25 Post: 13(↓48%) | Quality of life: QLQ-C3 (Global Health status): BCHY-15Gy: Pre: 34 Post: 62 (↑82%) QLQ-C3 (Physical Functioning): BCHY-15Gy: Pre: 56 Post: 78 (↑39%) QLQ-LC13 (Symptom Scale: Dyspnea) BCHY-15Gy: Pre: 33 Post: 13 (↓61%) |
| | | QLQ-LC13 (Symptom Scale: Cough) |

| Study | Intervention Group 1 | Intervention Group 2 |
|-------|---|---|
| | QLQ-LC13 (Symptom Scale: Cough) EBRT+BCHY-16Gy: Pre: 67 Post: 40 (↓40%) EBRT+BCHY-10Gy: Pre: 65 Post: 36 (↓45%) | BCHY-15Gy: Pre: 56 Post: 22 (↓61%) |
| | QLQ-LC13 (Symptom Scale: Hemoptysis) EBRT+BCHY-16Gy: Pre: 20 Post: 0 (↓100%) EBRT+BCHY-10Gy: Pre: 47 Post: 9 (↓81%) | QLQ-LC13 (Symptom Scale: Hemoptysis) BCHY-15Gy: Pre: 27 Post: 9 (↓67%) |
| | Performance status: Not reported | Performance status: Not reported |
| | Others: Dyspnea (% incidence) EBRT+BCHY-16Gy: Pre: 15 (100) Post: 14 (93) (NSS) EBRT+BCHY-10Gy: Pre: 13 (87) Post: 12 (92) (NSS) Dyspnea (median time to relapse in months) EBRT+BCHY-16Gy: 4 EBRT+BCHY-10Gy: 5 Dyspnea (median time to progression in months) EBRT+BCHY-16Gy: 7 EBRT+BCHY-10Gy: 7 Cough (% incidence) EBRT+BCHY-16Gy: Pre: 15 (100) Post: 12 (80) (NSS) EBRT+BCHY-10Gy: Pre: 15 (100) Post: 13 (87) (NSS) Cough (median time to relapse in months) EBRT+BCHY-16Gy: 4 EBRT+BCHY-10Gy: 7 Cough (median time to progression in months) EBRT+BCHY-16Gy: 7 EBRT+BCHY-10Gy: not reached Hemoptysis (% incidence) EBRT+BCHY-16Gy: Pre: 9 (60) | Others: Dyspnea (% incidence) BCHY-15Gy: Pre: 15 (100) Post: 13 (87) (NSS) Dyspnea (median time to relapse in months) BCHY-15Gy: 6 (NSS) Dyspnea (median time to progression in months) BCHY-15Gy: 6 (NSS) Cough (% incidence) BCHY-15Gy: Pre: 15 (100) Post: 13 (87) (NSS) Cough (median time to relapse in months) BCHY-15Gy: 4 (NSS) Cough (median time to progression in months) BCHY-15Gy: not reached (NSS) Hemoptysis (% incidence) BCHY-15Gy: Pre: 12 (80) Post: 10 (82) (NSS) |

| Study | Intervention Group 1 | Intervention Group 2 |
|-----------------------|--|---|
| | Post: 9 (100) (NSS) EBRT+BCHY-10Gy: Pre: 13 (87) Post: 13 (100) (NSS) Hemoptysis (median time to relapse in months) EBRT+BCHY-16Gy: 8 EBRT+BCHY-10Gy: not reached Hemoptysis (median time to progression in months) EBRT+BCHY-16Gy: 11 EBRT+BCHY-10Gy: not reached | Hemoptysis (median time to relapse in months) BCHY-15Gy: 5 (p=0.01) Hemoptysis (median time to progression in months) BCHY-15Gy: 6 (p=0.01) |
| Petera-2001, #2914 | Lung function: Not reported Obstructive symptoms: BCHY (Cur): Improvement in dyspnea: 11 (61%) Cough: 7 (44%) Hemoptysis: 4 (67%) BCHY (Pall): Improvement in dyspnea: 14 (74%) Cough: 12 (70%) Hemoptysis: 5 (71%) Quality of life: Not reported Performance status: Not reported Others: None | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: None |
| Stout-2000, #3640 | Lung function: Not reported BCHY: Obstructive symptoms: (% of +ve symptom endpoints) 4 weeks: Cough: 59% (n=41) Hemoptysis: 85% (n=41) Breathlessness : 78% (n=41) 8 weeks: Cough: 50% (n=46) Hemoptysis: 78% (n=46) Breathlessness: 59% (n=46) Quality of life: Not reported Performance status: Not reported | Lung function: Not reported EBRT: Obstructive symptoms: (% of +ve symptom endpoints) 4 weeks: Cough: 59% (n=29) Hemoptysis: 90% (n=29) Breathlessness : 66% (n=29) 8 weeks: Cough: 67% (n=46) Hemoptysis: 89% (n=46) Breathlessness: 78% (n=46) Quality of life: Not reported Performance status: Not reported |

| Study | Intervention Group 1 | Intervention Group 2 |
|-----------------------|--|---|
| | Others: (Global palliation) BCHY: 76% | Others: EBRT: 91% (0.09) |
| van Boxem-1999, #427 | Lung function: Not reported Obstructive symptoms: YAGL: 10 (71%) (on a yes no dichotomous scale as rated by study authors) Quality of life: Not reported Performance status: Not reported Others: Not reported | Lung function: Not reported Obstructive symptoms: ECAU: 13 (76%) Quality of life: Not reported Performance status: Not reported Others: Not reported |
| Vucicevic-1999, #4010 | Lung function: Not reported Obstructive symptoms: BCHY + EBRT: Dyspnea: Pre: 26/39 (67%) Post: 3/39 (8%) Cough: Pre: 35/39 (90%) Post: 8/39 (21%) Hemoptysis Pre: 22/39 (56%) Post: 1/39 (3%) Massive hemoptysis Pre: 6/39 (15%) Post: 0/39 (0%) Quality of life: Not reported Performance status: Not reported Others: None | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: NA Others: None |
| Weinberg-2010, #4066 | Lung function: Not reported Obstructive symptoms: Not reported Quality of life: Not reported Performance status: | Lung function: NA Obstructive symptoms: NA Quality of life: NA Performance status: |

| Study | Intervention Group 1 | Intervention Group 2 |
|--------------|-----------------------------|-----------------------------|
| | Not reported | NA |
| | Others: None | Others: NA |

Appendix Table C17. Toxicity outcomes of studies that address Key Question 3

| Study | Intervention Group 1 | Intervention Group 2 |
|-------------------------|---|--|
| Allison-2004, #108 | Not reported | NA |
| Chella-2000, #654 | YAGL + BCHY: Death due to hemoptysis: 1 (7%) (12 months after Rx) | YAGL Not reported |
| Celebioglu-2002, #604 | BCHY: Hemoptysis requiring hospitalization: 1 (1%) Pneumothorax: 0 Fistula: 0 Cardiovascular problems: 0 | NA |
| Celikoglu-2006, #606 | Not reported | NA |
| Chhajed-2006, #696 | STNT + LASR Stent migration: 3 (6%) Mucous plugging of the airway stent: 2 (4%) Moderate-to-severe bleeding during bronchoscopy: 1 (2%) Death within 24 h of the procedure: 1 (2%) | NA |
| Guilcher-2011, #188 | Respiratory insufficiency during HDR BCHY: 2 (1%) Grade III mucositis: 2 (1%) Grade II radiation bronchitis: 28 (12%) Pneumothorax: 3 (1%) Bronchial stenosis: 21 (9%) Necrosis of bronchial wall: 7 (3%) Hemoptysis: 15 (7%) Death due to complication: 13 (6%) Death due to hemoptysis: 10 (4%) Death due to necrosis: 2 (1%) Death due to radiation stenosis: 1 (0.4%) | NA |
| Jimenez-1999, #978 | PHDT Death from hemoptysis and presumed progression of the disease: 1(7%) | YAGL Death from hemoptysis and presumed progression of the disease: 1 6%) |
| Jones-2001, #1862 | Not reported | NA |
| Langendjik-2001, #2144 | EBRT +BCHY: Death due to massive hemoptysis: 7(15%) Broncho-esophageal fistula: 1 (2%) | BCHY: Death due to massive hemoptysis: 6(13%) |
| Lencioni-2008, #2238 | 40 procedures were done in NSCLC patients and there were 5 large or symptomatic pneumothorax needing drainage as a major complication. | |
| Moghissi-1999, #2591 | Not reported | Not reported |
| Muto-2000, Italy, #2665 | Grade 2 Radiation Bronchitis: BCHY (10 Gy): 13/78 (17%) BCHY (14Gy) + EBRT: 4/46 (9%) BCHY (15Gy, 1cm) + EBRT: 0/36 (0%) BCHY (15Gy, 0.5 cm) + EBRT: 3/120 (3%) Grade 3 Radiation Bronchitis: BCHY (10 Gy): 17/78 (22%) BCHY (14Gy) + EBRT: 3/46 (7%) | |

| Study | Intervention Group 1 | Intervention Group 2 |
|-----------------------|--|---|
| | BCHY (15Gy, 1cm) + EBRT: 3/36 (8%) BCHY (15Gy, 0.5 cm) + EBRT: 5/120 (4%) Grade 4 Radiation Bronchitis: BCHY (10 Gy): 12/78 (15%) BCHY (14Gy) + EBRT: 3/46 (7%) BCHY (15Gy, 1cm) + EBRT: 3/36 (8%) BCHY (15Gy, 0.5 cm) + EBRT: 5/120 (4%) Fatal hemoptysis: BCHY (10 Gy): 2/78 (3%) BCHY (14Gy) + EBRT: 3/46 (7%) BCHY (15Gy, 1cm) + EBRT: 2/36 (6%) BCHY (15Gy, 0.5 cm) + EBRT: 3/120 (3%) Broncho esophageal fistulas: BCHY (10 Gy): 1/78 (1%) BCHY (14Gy) + EBRT: 1/46 (2%) BCHY (15Gy, 1cm) + EBRT: 1/36 (3%) BCHY (15Gy, 0.5 cm) + EBRT: 0 (0%) | |
| Mallick-2006, #2417 | No grade II-grade IV acute complications occurred | No grade II-grade IV acute complications occurred 1 patient died due to fatal hemoptysis at 7 months |
| Petera-2001, #2914 | Not discernible | NA |
| Stout-2000, #3640 | BCHY: Fatal hemoptysis: 4 (8%) | EBRT: Fatal hemoptysis: 3 (6%) |
| Study | Intervention Group 1 | Intervention Group 2 |
| van Boxem-1999, #427 | YAGL: Hypotension: 1 (7%) | ECAU: Hemoptysis/respiratory failure: 1 (6%) |
| Vucicevic-1999, #4010 | Acute Esophagitis: 3/39 (8%) Cardiac arrhythmia: 1/39 (3%) Chronic Pulmonary fibrosis: 4/39 (10%) Esophageal stricture: 1/39 (3%) Fistulae: 1/39 (3%) Massive hemoptysis: 1/30 (3%) | NA |
| Weinberg-2010, #4066 | Bronchial contraction: 5/9 (56%) Occlusion from bronchial contraction: 2/9 (22%) Photosensitivity: 2/9 (22%) | NA |

Appendix Table C18. Study attributes - Key Question 3

| Study | HC | Enroll Start | Enroll End | Time | Study Setting | Treatment Setting | Institution Setting(s) | Stage(s): | Staging Criteria: | COI | Funding |
|-----------------------|-----|--------------|------------|------|---------------|-------------------|---------------------------------|--|------------------------------------|-----|----------------------|
| Allison-2004, | Yes | NR | NR | PRO | SI | O | TH | Recurrence | NR | No | NR |
| Celebioglu-2002, | Yes | 05/97 | 03/99 | RET | SI | I | TH | Stage 3,Stage 4,Recurrence | Int. Staging System of Lung Cancer | NR | NR |
| Celikoglu-2006, | Yes | NR | NR | PRO | SI | O | TH | Stage 3 | AJCC | NR | NR |
| Chella-2000, | Yes | Dec-95 | Dec-98 | PRO | SI | O | TH | NR | NR | NR | NR |
| Chhajed- 2006, | No | NR | NR | RET | SI | NR | TH | NR | NR | No | NR |
| Guilcher-2011, | No | 1991 | 2004 | RET | M | NR | Other : Unable to make judgment | NR | NR | No | NR |
| Jimenez-1999, | Yes | NR | NR | PRO | SI | NR | Other : Hospital | Stage 1,Stage 2,Stage 3,Stage 4,Recurrence | NR | NR | Manufacturer |
| Jones-2001, | Yes | 08/1998 | 12/2000 | RET | SI | I | TH | Stage 3,Stage 4 | NR | NR | NR |
| Langendjik-2001, | Yes | NR | NR | PRO | M | NR | TH | Stage 1,Stage 3 | UICC 1992 | No | Professional Society |
| Lencioni-2008, | Yes | 07/2001 | 12/2005 | PRO | M | NR | TH | Stage 1, Recurrence | NR | No | Manufacturer |
| Mallick- 2006, # 2417 | Yes | 05/2003 | 02/2005 | PRO | SI | O | TH | Stage 3 | NR | No | Not supported |
| Moghissi-1999, | Yes | 05/1993 | 11/1996 | PRO | MI | O | CH, CC | NR | NR | NR | NR |
| Muto-2000, | Yes | 01/1992 | 07/1997 | PRO | SI | NR | TH | Stage 3 | NR | NR | NR |
| Petera-2001, | No | 12/1996 | 04/1999 | NR | SI | NR | TH | Stage 2,Stage 3,Stage 4 | NR | NR | NR |
| Stout-2000, | Yes | 07/1989 | 07/1993 | PRO | M | O | CH | NR | NR | NR | NR |
| van Boxem-1999, | Yes | 01/94 | 12/96 | RET | SI | I | TH | Stage 3,Stage 4 | NR | NR | NR |
| Vucicenic-1999, | Yes | 01/1996 | 12/1997 | RET | SI | NR | TH | Stage 3 | NR | NR | NR |
| Weinberg-2010, | Yes | 1/2001 | 8/2008 | NR | SI | NR | TH | Stage 1,Stage 2,Stage 3,Stage 4 | NR | NR | NR |

Appendix Table C19. Carey and Boden assessment tool for Key Questions 1 and 2

| ID | KQ | Clearly Defined Question | Well-described study population | Well-described intervention | Use of Validated Outcome Measures | Appropriate Statistical Analysis | Well-Described Results | Discussion/Conclusions Supported by Data | Funding/Sponsor Source Acknowledged |
|-------------------|-------|--------------------------|---------------------------------|-----------------------------|-----------------------------------|----------------------------------|------------------------|--|-------------------------------------|
| Andratschke, 2011 | KQ1 | Y | Y | Y | Y | U | Y | U | Y |
| Baumann, 2006 | KQ1 | N | Y | Y | Y | Y | Y | Y | N |
| Baumann, 2009 | KQ1 | Y | Y | Y | Y | Y | Y | Y | Y |
| Bogart, 2010 | KQ1 | Y | N | N | Y | Y | Y | Y | Y |
| Bollineni, 2012 | KQ1 | Y | Y | N | Y | Y | Y | U | Y |
| Bradley, 2003 | KQ1 | Y | Y | Y | Y | Y | Y | Y | N |
| Burdick, 2010 | KQ1 | Y | Y | Y | Y | Y | Y | Y | N |
| Bush, 2004 | KQ1 | Y | Y | Y | Y | Y | Y | Y | Y |
| Campeau, 2009 | KQ1 | Y | Y | Y | Y | Y | Y | Y | N |
| Chen, 2012 | KQ2 | Y | Y | N | Y | Y | N | U | N |
| Coon, 2008 | KQ1 | Y | Y | Y | Y | N | Y | Y | N |
| Dunlap, 2010 | KQ1 | Y | Y | Y | Y | Y | Y | Y | N |
| Fritz, 2008 | KQ1 | Y | Y | Y | Y | Y | Y | Y | N |
| Graham, 2006 | KQ1 | Y | Y | Y | Y | Y | Y | Y | N |
| Iwata, 2010 | KQ1/2 | Y | Y | Y | Y | Y | Y | Y | Y |
| Jimenez, 2010 | KQ1 | Y | Y | Y | Y | Y | N | U | N |
| Kopek, 2009 | KQ1 | Y | Y | Y | Y | Y | Y | Y | Y |
| Mirri, 2009 | KQ1 | Y | N | Y | Y | U | N | U | N |
| Nakayama, 2010 | KQ1 | Y | Y | N | Y | Y | N | U | N |
| Narayan, 2004 | KQ1 | Y | N | Y | Y | Y | N | U | Y |

| ID | KQ | Clearly Defined Question | Well-described study population | Well-described intervention | Use of Validated Outcome Measures | Appropriate Statistical Analysis | Well-Described Results | Discussion/Conclusions Supported by Data | Funding/Sponsor Source Acknowledged |
|-----------------------------|-------|--------------------------|---------------------------------|-----------------------------|-----------------------------------|----------------------------------|------------------------|--|-------------------------------------|
| Nyman, 2006 | KQ1 | Y | Y | Y | Y | Y | Y | Y | N |
| Olsen, 2011 | KQ1 | Y | N | Y | Y | Y | Y | U | N |
| Palma, 2011 | KQ1 | Y | N | Y | Y | Y | Y | U | Y |
| Pennathur, 2007 | KQ1 | Y | Y | Y | Y | Y | Y | Y | Y |
| Pennathur, 2009 | KQ1 | Y | Y | Y | Y | Y | Y | Y | N |
| Ricardi, 2010 | KQ1 | Y | Y | Y | Y | Y | Y | N | N |
| Scorsetti, 2007 | KQ1 | N | Y | Y | Y | Y | Y | Y | N |
| Shibamoto, 2012 | KQ1/2 | Y | Y | Y | Y | Y | Y | Y | Y |
| Song, 2009 | KQ1 | Y | Y | Y | Y | Y | Y | Y | Y |
| Stephans, 2009 | KQ1 | Y | Y | Y | Y | Y | Y | Y | Y |
| Takeda, 2009 | KQ1/2 | Y | Y | Y | Y | Y | Y | Y | N |
| Taremi, 2011 | KQ1 | Y | N | Y | Y | Y | Y | Y | Y |
| Turzer, 2011 | KQ1 | Y | Y | Y | Y | Y | Y | Y | N |
| Vahdat, 2010 | KQ1 | Y | N | Y | Y | Y | N | N | N |
| van der Voort van Zyp, 2009 | KQ1 | Y | N | Y | Y | Y | Y | Y | N |
| Videtic, 2010 | KQ1 | Y | Y | Y | Y | Y | Y | Y | N |
| Lagerwaard, 2011 | KQ2 | Y | Y | N | Y | Y | Y | Y | N |

| ID | KQ | Clearly Defined Question | Well-described study population | Well-described intervention | Use of Validated Outcome Measures | Appropriate Statistical Analysis | Well-Described Results | Discussion/Conclusions Supported by Data | Funding/Sponsor Source Acknowledged |
|--------------|-----------|---------------------------------|--|------------------------------------|--|---|-------------------------------|---|--|
| Onishi, 2011 | KQ2 | Y | Y | Y | Y | Y | Y | Y | Y |

Appendix Table C20. Carey and Boden assessment tool for Key Question 3

| ID | KQ | Clearly Defined Question | Well-described study population | Well-described intervention | Use of Validated Outcome Measures | Appropriate Statistical Analysis | Well-Described Results | Discussion/Conclusions Supported by Data | Funding/Sponsor Source Acknowledged |
|----------------|-----------|---------------------------------|--|------------------------------------|--|---|-------------------------------|---|--|
| Allison, 2004 | 3 | Y | Y | Y | Y | N | Y | Y | N |
| Chhajed, 2006 | 3 | N | N | N | Y | Y | N | N | N |
| Lencioni, 2008 | 3 | Y | Y | Y | N | N | Y | N | Y |

Abbreviations Used in This Appendix

| 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 |
| CSS | 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 | Gray |
| 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 <i>scales</i> |
| 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 | Radio-frequency 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 |