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Screening for Lung Cancer With Low-Dose Computed Tomography: An Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Purpose: To systematically review the evidence on effectiveness, accuracy, and harms of screening for lung cancer with low-dose computed tomography (LDCT) for populations and settings relevant to primary care in the United States.

Data Sources: PubMed/MEDLINE, the Cochrane Library, and trial registries through May 28, 2019; reference lists of retrieved articles; outside experts; and reviewers, with surveillance of the literature through November 20, 2020.

Study Selection: English-language controlled trials of screening for lung cancer with LDCT; studies evaluating LDCT screening accuracy; studies of risk prediction models comparing benefits and harms of screening vs. the use of trial eligibility criteria or 2013 U.S. Preventive Services Task Force recommendations; trials and prospective cohort studies of treatment for Stage I lung cancer with surgery or stereotactic body radiotherapy reporting at least 5-year survival; prospective cohort and case-control studies reporting harms.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated quality for all included studies using predefined criteria.

Data Synthesis: This review included 223 publications. Seven randomized, controlled trials (RCTs) (described in 26 articles; 86,486 participants) evaluated lung cancer screening with LDCT; the National Lung Screening Trial (NLST) and Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) were the only RCTs that were adequately powered. The NLST found a reduction in lung cancer mortality (calculated incidence rate ratio [IRR], 0.85 [95% confidence interval {CI}, 0.75 to 0.96]) and all-cause mortality (calculated IRR, 0.93 [95% CI, 0.88 to 0.99]) with three rounds of annual LDCT screening compared with chest X-ray for high-risk current and former smokers ages 55 to 74 years. These findings indicate a number needed to screen (NNS) to prevent one lung cancer death of 323 over 6.5 years of followup. NELSON found a reduction in lung cancer mortality (calculated IRR, 0.75 [95% CI, 0.61 to 0.90]) but not all-cause mortality (calculated IRR, 1.01 [95% CI, 0.92 to 1.11]) with four rounds of LDCT screening with increasing intervals (at baseline, 1 year, 3 years, and 5.5 years) compared with no screening for high-risk current and former smokers ages 50 to 74 years. These findings indicate an NNS to prevent one lung cancer death of 130 over 10 years of followup. The sensitivity of LDCT ranged from 59 to 100 percent (13 studies; n=76,856) and was over 80 percent in most studies. The specificity ranged from 26.4 to 99.7 percent (13 studies; n=75,819) and was over 75 percent in most studies. The positive predictive value (PPV) ranged from 3.3 to 43.5 percent. The negative predictive value ranged from 97.7 to 100 percent. Evidence suggests that using the Lung-RADS™ classification system in the NLST would have increased specificity while decreasing sensitivity and increasing nodule size threshold for a positive screening result would increase PPV. Harms of screening included radiation-induced cancer (estimated 0.26 to 0.81 major cancers for every 1,000 people screened with 10 annual LDCTs), false-positive results leading to unnecessary tests and invasive procedures, overdiagnosis, incidental findings, and short-term increases in distress because of indeterminate results. For every 1,000 persons screened in the NLST, false-positive results led to 17 invasive procedures (number needed to harm, 59), resulting in less than one major complication. Using Lung-RADS could reduce false-

positive results compared with the NLST criteria; estimates suggest that using Lung-RADS could have prevented about 23 percent of all invasive procedures for false positives in the NLST. Overdiagnosis estimates ranged from a 0 to 67 percent chance that a screen-detected lung cancer was overdiagnosed. The NLST data indicate approximately four cases of overdiagnosis (and 3 lung cancer deaths prevented) per 1,000 people screened over 6.5 years. Incidental findings were common and variably defined with a wide range reported across studies (4.4% to 40.7% of people screened).

Modeling studies estimated that using risk prediction models would increase the number of screen-preventable deaths, reduce the number of participants needed to screen to prevent one lung cancer death, and reduce the number of false positive selections (i.e., selecting persons to be screened who did not have or develop lung cancer or death from lung cancer) per prevented lung cancer death compared with risk factor–based screening, when NLST-like cancer detection and mortality reductions were assumed, but the strength of evidence was low because it was largely derived from post hoc application to trial data and modeling.

Limitations: NLST and NELSON participants were younger, more highly educated, and less likely to be current smokers than the U.S. screening-eligible population, and they had limited racial and ethnic diversity. The general U.S. population eligible for lung cancer screening may be less likely to benefit from early detection compared with the NLST and NELSON participants because they face a higher risk of death from competing causes and the NLST and NELSON were mainly conducted at large academic centers, potentially limiting applicability to community-based practice. Most studies reviewed in this report (including the NLST) did not use current nodule evaluation protocols such as Lung-RADS.

Conclusions: Screening high-risk persons with LDCT can reduce lung cancer mortality and may reduce all-cause mortality but also causes false-positive results leading to unnecessary tests and invasive procedures, overdiagnosis, incidental findings, increases in distress, and, rarely, radiation-induced cancers. The evidence for benefits comes from two RCTs that enrolled participants who were more likely to benefit than the U.S. screening-eligible population and that were mainly conducted at large academic centers, potentially limiting applicability to community-based practice. Application of lung cancer screening with current nodule management protocols (e.g., Lung-RADS) might improve the balance of benefits and harms. Use of risk prediction models might improve the balance of benefits and harms, although there remains considerable uncertainty about how such approaches would perform in actual practice because current evidence does not include prospective clinical utility studies.

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Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF) will use this report to inform an update of its recommendation on the topic of lung cancer screening. In 2013, the USPSTF recommended annual screening for lung cancer with low-dose computed tomography (LDCT) in adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years (B recommendation).[1] The USPSTF recommended that screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. This report systematically evaluates the current evidence on screening for lung cancer with LDCT for populations and settings relevant to primary care in the United States. This report also summarizes the main benefits and harms of surgical resection or stereotactic body radiotherapy (SBRT) for the treatment of early (Stage I) non-small cell lung cancer (NSCLC).

Condition Definition

Lung cancer is an abnormal proliferation of cells that originate in the lung tissues. Lung cancer has traditionally been classified into two major categories based on cell type and incorporation of immunohistochemical and molecular characteristics: (1) NSCLC, which collectively comprises adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, and (2) small-cell lung cancer (SCLC), which is more aggressive and has worse survival rates.[2] The Tumor Node Metastasis staging system is used to characterize the extent of disease and determine lung cancer stage, treatment, and prognosis. **Table 1** shows an overview of staging for NSCLC. Persons with Stage I disease have lung tumors less than or equal to 4 cm, no lymph node or metastatic involvement, and the best prognosis for survival.[3] For SCLC, a simpler staging designating limited and extensive disease is used.

Etiology and Natural History

Smoking is the number one cause of lung cancer, but secondhand smoke and environmental exposures also increase risk.[4] Trends in lung cancer incidence and mortality rates have closely reflected historical patterns of smoking (but with a delay of decades).[4] In general, the prognosis for persons with lung cancer is poor; the 5-year survival rate for all stages combined was about 16 percent from 1995 to 2001, with rates varying significantly by stage at diagnosis.[5] From 2008 to 2014, reported 5-year survival rates were better, 18.6 percent for all stages combined.[3] Most patients (79%) diagnosed with lung cancer present with distant or metastatic disease; only 16 percent are diagnosed with localized (i.e., Stage 1) disease.[3]

Risk Factors

The risk of developing lung cancer is largely driven by age and smoking status. The incidence of lung cancer increases with every additional decade of life; the median age of lung cancer diagnosis is 70 years.[6, 7] Smoking is estimated to account for nearly 90 percent of all lung cancers.[8] The relative risk of lung cancer in smokers is approximately 20-fold that of nonsmokers, and risk increases with cumulative quantity and duration of smoking.[9] Secondhand smoke, which exposes nonsmokers to the components of tobacco smoke at lower concentrations, is also an established cause of lung cancer.[10, 11]

Other risk factors for lung cancer include environmental exposures, radiation therapy, other (noncancer) lung diseases, race/ethnicity,[12] and family history. Environmental exposures account for a proportionately smaller burden of lung cancer compared with tobacco (approximately 10%) and include the carcinogens radon, asbestos, polycyclic aromatic hydrocarbons (i.e., tar, soot), arsenic, and metals (e.g., beryllium, cadmium, chromium, nickel).[13, 14] Patients treated with radiation therapy are also at an increased risk of developing a primary lung cancer. In a systematic review that included 21 studies of patients with Hodgkin's lymphoma, radiation therapy was associated with an approximately five-fold increase in secondary lung cancer; the percentage of patients who received radiation therapy ranged from 48 to 100 percent in the included studies.[15] Similarly, in a meta-analysis of breast cancer patients (N=631,021), those treated with radiation therapy had a higher risk of a second lung cancer (relative risk [RR], 1.23; 95% confidence interval [CI], 1.07 to 1.43), which increased with duration of time following diagnosis.[16] Lung diseases, such as chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis, are associated with an increased risk of lung cancer, independent of age and smoking history.[17] In a subcohort analysis of the National Lung Screening Trial (NLST), lung cancer incidence increased linearly with increasing severity of COPD.[18] Cigarette smoking potentiates the risk of lung cancer in persons with other risk factors like environmental exposures, radiation therapy, and lung disease.[18-20] Finally, a family history of lung cancer is associated with a 1.7-fold increased risk of developing lung cancer (95% CI, 1.6 to 1.9), an association that is greater with two or more relatives with lung cancer and weaker in nonsmokers (odds ratio [OR], 3.6 [95% CI, 1.6 to 83] and OR, 1.4 [95% CI, 1.2 to 1.7], respectively).[21]

Prevalence and Burden

Lung cancer is the second most common cancer and the leading cause of cancer-related death in both men and women in the United States.[22] In 2017 (the most recent year with complete data) 222,500 persons in the United States were diagnosed with lung cancer, and 155,870 persons died from lung cancer, of which 84,590 were men and 71,280 were women.[22] A large majority (approximately 85%) of lung cancers are NSCLC, about 10 to 15 percent of lung cancers are SCLC, and fewer than 5 percent are lung carcinoid tumors.[23] Lung cancer incidence increases with age, and the risk is greater in men than in women. Among men, black men have the highest incidence rate of getting lung cancer, followed by white, Asian/Pacific Islander, American Indian/Alaska Native, and Hispanic men.[3] Among women, the rate is highest among white women, followed by black, American Indian/Alaska Native, Asian/Pacific Islander, and Hispanic

women.[3] Lung cancer incidence and death rates have decreased since the 1990s in both men and women because of lower rates of smoking.[3, 22]

Regarding the preventable burden of disease, a 2013 study using National Health and Nutrition Examination Survey and National Health Interview Survey (NHIS) data estimated that approximately 8.6 million Americans were eligible for lung cancer screening in 2010 according to NLST eligibility criteria (ages 55 to 74 years with at least a 30 pack-year smoking history who currently smoke or used to smoke). The study stated that if the NLST were fully implemented among this screening-eligible population, a total of 12,250 lung cancer deaths would be averted each year.[24] Others have estimated fewer lung cancer deaths would be averted. A study using data from the 2012 Health and Retirement Study evaluated comorbidities, life expectancy, smoking history, and other characteristics in the screening-eligible population and in NLST participants; it reported a lower 5-year survival rate and life expectancy in the screening-eligible persons compared with NLST participants. The authors concluded that the general U.S. population eligible for lung cancer screening is probably less likely to benefit from early detection compared with NLST participants because they face a high risk of death from competing causes, such as heart disease, diabetes, or stroke.[25]

Rationale for Screening and Screening Strategies

Lung cancer has a high prevalence, high morbidity and mortality, and better survival rates if diagnosed at an earlier stage.[3] The main rationale for screening is that it could lead to earlier detection of lung cancer when treatment is more likely to be effective. Screening is aimed at early detection of NSCLC rather than SCLC because the latter is much less common and typically spreads too quickly to be reliably detected by intermittent screening. The screening modality used in current clinical practice is LDCT. Other screening modalities that have been studied, but have not found to be beneficial, include sputum cytology, chest X-ray (CXR), and biomarkers.[26, 27]

Findings from LDCT can range from incidental pulmonary nodules to lesions suspicious for lung cancer. Multiple approaches to nodule classification that guide additional testing or surveillance are available. For example, in an effort to standardize LDCT screening results reporting, the American College of Radiology developed and endorses the Lung-RADS™ classification system (**Appendix A Table 1** and **Appendix A Table 2**).[28] Lung-RADS provides guidance to clinicians on which findings are suspicious for cancer and suggested management. Briefly, lesions in Lung-RADS categories 1 and 2 are considered benign, whereas category 3 lesions (probably benign) warrant more frequent surveillance, and category 4 lesions (suspicious) require more aggressive evaluation.

For patients with suspected lung cancer, diagnosis by the least invasive method is recommended.[29] Choosing a method to establish a diagnosis of lung cancer depends on the location of the primary lesion and potential metastatic lesions. Diagnostic techniques and procedures include sputum cytology; flexible bronchoscopy, preferred for central lesions; endobronchial ultrasound, preferred for peripheral lesions; trans-thoracic tissue needle aspiration for lesions not accessible by bronchoscopy; pleural fluid cytology or biopsy for pleural lesions;

and surgery. If results from any method are negative and clinical suspicion is high, more invasive testing is recommended.

Treatment Approaches

Lung cancer can be treated with surgery, chemotherapy, radiation therapy, newer targeted immunotherapies, and combinations of these treatments.[30] Management is determined by the presenting stage of disease and the patient's functional status, pulmonary function, medical comorbidities, and values (**Table 1** for NSCLC; **Appendix A Table 3** for SCLC). Surgical resection, lobectomy, is the treatment of choice for eligible patients with Stage I or II NSCLC and can be performed via open thoracotomy or video-assisted thoracoscopic surgery (VATS).[31] For nonsurgical candidates, SBRT is a treatment option. In the NLST and NELSON trials, 50 to 62 percent of diagnosed cancers in the LDCT screening group were Stage I and 6 to 7 percent were Stage II (**Appendix A Table 4**).[32, 33]

Clinical Practice in the United States

Several recent studies have described the uptake of lung cancer screening in the United States since the USPSTF B recommendation was issued. An analysis of data from the Cancer Control Module of the NHIS data from 2010 (before the most recent USPSTF guidelines were issued) and 2015 (after the guidelines were issued) gives some idea of screening uptake.[34] The NHIS survey used the following item as a proxy for lung cancer screening with chest computed tomography (CT): "Were any of the CAT scans of your chest area done to check for lung cancer, rather than for some other reason?" Overall, the percentage of U.S. adults older than age 40 who received CT scans for lung cancer screening was very low, although it increased from 2010 to 2015 (1.3% vs. 2.1%). Among respondents who met USPSTF-recommended age and smoking criteria, screening increased from 2.1 to 6.0 percent ($p<0.001$). The survey also found a temporal increase in screening from 2.1 to 3.8 percent among 55- to 74-year-olds who were at lower risk for lung cancer because they did not meet the eligibility criteria for smoking ($p<0.001$). Overall, the findings suggest an increase, which was large in relative terms but small in absolute terms, in use of CT screening in the U.S. population meeting eligibility criteria for lung cancer screening as well as some "unintended spillover" of screening to lower risk populations. An analysis using a 20 percent national sample of Medicare enrollees ages 55 to 77 years from January 2010 through December 2016 estimated even lower rates of LDCT screening than those estimated from NHIS.[35] More recently, however, a study using data for 10 states from the 2017 Behavioral Risk Factor Surveillance System survey found that uptake of LDCT was up to 14.4 percent, with variation across the 10 states (from 6.5% to 18.1%) and higher rates for those with insurance or COPD.[36]

A recent survey of medical directors of Federally Qualified Health Centers that serve low-income populations found that 43 percent of clinics had implemented lung cancer screening, although most reported low volume. Respondents noted that substantial implementation challenges include lack of staff time, lack of resources to systematically collect tobacco use data

and track screened populations, and substantial patient financial barriers to initial screening (for those uninsured) and followup procedures.[37]

A description of implementation of lung cancer screening in the Veterans Health Administration found that 2,106 patients underwent screening over 2 years.[38] The authors noted that screening registry data collection was labor intensive and required manual abstraction of medical record information. Of all patients screened, 56 percent had nodules that required tracking; 2 percent required further evaluation, but the findings were not cancer; and 1.5 percent had lung cancer. Incidental findings (e.g., emphysema, coronary artery calcification) were noted on LDCT scans of 40.7 percent of patients.[38, 39]

The Centers for Medicare & Medicaid Services (CMS) covers lung cancer screening, albeit with several stipulations.[40] Among these stipulations is a requirement for a written order from a provider during a lung cancer screening counseling and shared decision making (SDM) visit. Specific required elements of this visit included the use of one or more decision aids, to include benefits, harms, followup diagnostic testing, overdiagnosis, false positive rate, and total radiation exposure. Another stipulation was that CMS would cover screening only by radiologists and imaging facilities that meet certain quality standards and that collect and submit required data elements to a CMS-approved national registry for each LDCT lung cancer screening performed. Virtually all guidelines that recommend lung cancer screening, including those issued by the USPSTF, recommend that providers conduct a rigorous process of informed and SDM about the benefits and harms of lung cancer screening before initiating screening. However, given the complex nature of benefits and harms associated with screening, there is some concern that robust SDM is impractical to implement in actual practice.[37, 41, 42] Contextual Question 1 (**Appendix A**) further describes the barriers to implementing lung cancer screening and surveillance in clinical practice in the United States.

Recommendations of Other Organizations

Most guidelines on lung cancer screening now recommend screening in high-risk persons. The American Cancer Society, along with several specialty societies including the American Thoracic Society, the American College of Chest Physicians, and the American Lung Association, have issued recommendations that are similar to those of the USPSTF (**Appendix A Table 5**). The definition of high risk varies somewhat in terms of age range, smoking history, and other factors but is generally overlapping across guidelines. The National Comprehensive Cancer Network (NCCN) recommends expansion of the screening-eligible population beyond the USPSTF criteria by beginning at age 50 in those with 20 or more pack-years if they also have an additional risk factor, including a cancer history, family history, chronic lung disease (including COPD), or occupational/environmental exposures (e.g., asbestos, radon, silica). The NCCN also notes that it is reasonable to consider using the PLCOm2012 lung cancer risk calculator to assist in quantifying risk, considering a 1.3 percent threshold of lung cancer risk (over 6 years).[43] Of note, the American Academy of Family Physicians (AAFP) reviewed the USPSTF recommendation and concluded that evidence was insufficient[44] to recommend for or against screening.[45] They determined that screening cannot be recommended on the basis of a single study conducted in major medical centers.

Chapter 2. Methods

Key Questions and Analytic Framework

The scope and key questions (KQs) were developed by the Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers. The analytic framework and KQs that guided the review are shown in **Figure 1**. Eight KQs were developed for this review:

1. a. Does screening for lung cancer with LDCT change the incidence of lung cancer and the distribution of lung cancer types and stages (i.e., stage shift)?
   b. Does screening for lung cancer with LDCT change all-cause mortality, lung cancer mortality, or quality of life?
   c. Does the effectiveness of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?
   d. Does the effectiveness of screening for lung cancer with LDCT differ by the number or frequency of LDCT scans (e.g., annual screening for 3 years, the protocol used in the NLST vs. other approaches)?

2. Does the use of risk prediction models for identifying adults at higher risk of lung cancer mortality improve the balance of benefits and harms of screening compared with the use of trial eligibility criteria (e.g., NLST criteria) or the 2013 USPSTF recommendations?

3. a. What is the accuracy of screening for lung cancer with LDCT?
   b. Does the accuracy of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?
   c. Does the accuracy of screening for lung cancer with LDCT differ for various approaches to nodule classification (i.e., those based on nodule size and characteristics)?

4. a. What are the harms associated with screening for lung cancer with LDCT?
   b. Do the harms of screening for lung cancer with LDCT differ with the use of Lung-RADS, International Early Lung Cancer Action Program (I-ELCAP), or similar approaches (e.g., to reduce false-positive results)?
   c. Do the harms of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?

5. a. What are the harms associated with workup or surveillance of nodules?
   b. Do the harms of workup or surveillance of nodules differ with the use of Lung-RADS, I-ELCAP, or similar approaches (e.g., to reduce false-positive results)?
   c. Do the harms of workup or surveillance of nodules differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?

6. a. What is the effectiveness of surgical resection or SBRT for the treatment of early (Stage I) non-small cell lung cancer?
   b. Does the effectiveness of surgical resection or SBRT differ for subgroups defined by age, sex, race/ethnicity, or presence of comorbid conditions?

7. a. What are the harms associated with surgical resection or SBRT for the treatment of early (Stage I) non-small cell lung cancer?
   b. Do the harms of surgical resection or SBRT differ for subgroups defined by age, sex, race/ethnicity, or presence of comorbid conditions?

8. What is the magnitude of change in all-cause and lung cancer mortality that results from a specified change in lung cancer incidence (and change in distribution of lung cancer stages [i.e., stage shift]) after screening?

In addition to addressing the KQs, this review also looked for evidence related to four contextual questions (CQs) that focused on barriers to implementing lung cancer screening and surveillance in clinical practice in the United States; the representativeness of participants, settings, and providers in randomized, controlled trials (RCTs) of lung cancer screening to corresponding individuals and institutions in the United States.; the comparability of 5-year survival rates and life expectancy of screening-eligible adults (based on NSLT criteria or USPSTF recommendations) to those of NLST participants; unintended benefits of LDCT screening for lung cancer from detecting incidental findings; and the effectiveness of smoking cessation interventions among patients receiving LDCT screening. These CQs were not a part of this systematic review. They are intended to provide additional background information. Literature addressing these questions is summarized in **Appendix A**.

Data Sources and Searches

PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published from January 1, 2012, through May 28, 2019. A predefined list of search terms and Medical Subject Headings (MeSH) focused on terms that describe relevant populations, tests, interventions, outcomes, and study designs was used when applicable. The search relied primarily on the previous systematic review for the USPSTF to identify potentially relevant studies published before 2012 (we reassessed all articles included in that systematic review using the eligibility criteria).[46, 47] Complete search terms and limits are listed in **Appendix B**. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) were searched for unpublished literature. To supplement electronic searches, reference lists of relevant articles, systematic reviews, and studies meeting the inclusion criteria were reviewed. Studies suggested by peer reviewers or public comment respondents were reviewed and, if appropriate, incorporated into the final review. Since May 28, 2019, ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on November 20, 2020, and we identified two potentially relevant articles. One study used the LCDRAT risk prediction model using the NHIS 2013-2015. Findings were

similar to those reported by other studies assessing the LCDRAT that are included in this review.[48] The study also estimated life-years gained by screening by developing another model for risk prediction of mortality; however, the model was not externally validated in a non-NHIS cohort and was therefore not eligible for this review. The second article (also mentioned by a public commenter) was by the same authors and evaluated the LCDRAT model using NHIS 2005, 2010, and 2015.[49] It similarly estimated a greater percentage of screen-prevented lung cancer deaths across a range of risk thresholds (1.5% to 2.5%) compared with USPSTF criteria. The results of these studies would not change conclusions or the strength of evidence. All literature search results were managed using EndNote™ version 7.4 (Thomson Reuters, New York, NY).

Study Selection

Inclusion and exclusion criteria for populations, interventions, comparators, outcomes, timing, settings, and study designs were developed with input from the USPSTF (**Appendix B2**). English-language studies of adults age 18 years or older conducted in countries categorized as "very high" on the 2016 Human Development Index[50] and published in or after 2001 were included. For KQs 1 through 5 and 8 (screening and risk prediction), studies of asymptomatic adults with at least 1,000 participants were included. For KQs 6 and 7 (benefits and harms of treatment), studies among adults with Stage I NSCLC treated with surgery or SBRT (sometimes referred to as stereotactic ablative radiation, or SABR) were included. For all KQs, controlled clinical trials were eligible. Prospective cohort studies (i.e., cohort studies based on prospectively collected data that were intended to be used for evaluations relevant to this review) were also eligible for KQs on harms of screening or workup (KQs 4 and 5) and treatment (KQs 6 and 7); case-control studies were eligible for KQs on harms (KQs 4, 5, and 7).

For KQ 1 (direct evidence for health outcomes), studies that compared LDCT with CXR, no screening, or usual care were eligible. For KQ 2 (on risk prediction), externally validated models aimed at identifying persons at increased risk of lung cancer using multiple variables, including at least age and smoking history, were included. Eligible risk prediction models had to be compared to either the 2013 USPSTF recommendations or criteria used by trials showing benefit (e.g., NLST). Eligible outcomes included estimated screen-preventable lung cancer deaths or all-cause mortality, estimated screening effectiveness (e.g., number needed to screen [NNS]), and estimated screening harms. For KQ 3 (on accuracy), eligible outcomes included sensitivity, specificity, and predictive value. Because there is no single gold standard for assessing accuracy of LDCT for the diagnosis of lung cancer, comparators of subsequent diagnosis of lung cancer within 1 year (likely from repeat imagining and biopsy), biopsy, or subsequent imaging were eligible. For KQs on the harms of screening (KQ 4) or workup and surveillance (KQ 5), studies that evaluated LDCT (KQ 4) or other tests used after screening (KQ 5) were eligible; a comparison group was not required. For KQs on benefits (KQ 6) and harms (KQ 7) of treatment, studies that reported survival over at least 5 years of followup or harms were eligible.
Titles and abstracts were independently reviewed by two investigators; those marked for potential inclusion by either reviewer were retrieved for evaluation of the full text. The full texts were then independently reviewed by two investigators to determine final inclusion or exclusion. Disagreements were resolved by discussion and consensus.

Quality Assessment and Data Abstraction

Quality assessments were conducted using instruments devised for each of the included study designs and adapted for this topic. Criteria developed by the USPSTF[51] were used to evaluate randomized studies, while Cochrane's ROBINS-I tool[52] was used for nonrandomized studies, the QUADAS-2 instrument[53] was used to assess studies of diagnostic accuracy (KQ 3), and the CHARMS checklist[54] was used to assess risk prediction models (KQ 2) (**Appendix B)**. Each study was evaluated by two independent reviewers using the instrument(s) described above. Risk-of-bias ratings were translated into overall quality ratings of good, fair, or poor, using USPSTF criteria.[51] Disagreements were resolved by discussion. Only studies rated as having good or fair quality were included.

For each included study, one investigator extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings, and study designs. All data extractions were checked by a second investigator for completeness and accuracy.

Data Synthesis and Analysis

Findings for each KQ were summarized in tabular and narrative format. For KQs 4 and 5, it was often unclear whether harms were directly from LDCT screening or were part of the downstream workup that follows screening. Therefore, this review reports the harms of screening and the cascade of events that follows within a combined section for KQs 4 and 5 that was stratified by outcome (e.g., radiation, overdiagnosis), specifying, when possible, if harms were directly from a particular part of the cascade. The overall strength of the evidence for each KQ was assessed as high, moderate, low, or insufficient based on the overall quality of the studies, consistency of results between studies, precision of findings, risk of reporting bias, and limitations of the body of evidence, using methods developed for the USPSTF (and the EPC program).[51] Additionally, the applicability of the findings to U.S. primary care populations and settings was assessed. Discrepancies were resolved through consensus discussion.

To determine whether meta-analyses were appropriate, the clinical and methodological heterogeneity of the studies was assessed according to established guidance.[55] The populations, tests, treatments, comparators, outcomes, and study designs were assessed qualitatively, looking for similarities and differences. The authors of this review did not conduct meta-analyses because of substantial clinical and methodological heterogeneity. For example, the trials of lung cancer screening differed in eligibility criteria (e.g., age, pack-years of smoking, years since quitting), number of screening rounds (from 2 to 5), screening intervals (e.g., annual, biennial, or escalating), thresholds for a positive screen (e.g., 4 mm, 5 mm, or based on volume), and comparators (CXR or no screening). For KQ 1, the authors of this review created forest plots to display the findings of each study by calculating incidence rate ratios (IRR), using number of events and person-years, for lung cancer incidence, lung cancer mortality, and all-cause mortality. Quantitative analyses were conducted using Stata version 14 (Stata Corp).

USPSTF Involvement

This review was funded by AHRQ. AHRQ staff and USPSTF members participated in developing the scope of the work and reviewed draft reports, but the authors are solely responsible for the content.

Expert Review and Public Comment

A draft Research Plan was posted for public comment on the USPSTF Web site from May 3, 2018 to May 30, 2018. In response to public comments, the USPSTF expanded the eligibility criteria to include SBRT and clarified terminology related to screening tests, comparators, and outcomes in the Research Plan. A final Research Plan was posted on the USPSTF's Web site on August 16, 2018. A draft report was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers. Reviewer comments were presented to the USPSTF during its deliberations and subsequently addressed in revisions of this report when appropriate. The draft report was posted for public comment. Revisions were made based on comments received, and references suggested by expert or public reviewers were evaluated for inclusion/exclusion. Revisions included the addition of a study addressing variation in accuracy by different approaches to nodule classification, clarifying that I-ELCAP changed their threshold for a positive nodule over time (from 5 mm to 6 mm), clarifying the nonlung cancers diagnosed in NLST participants, and updating the risk factors section of the introduction.

Chapter 3. Results

Literature Search

We identified 11,541 unique records and assessed 2,212 full-text articles for eligibility (**Figure 2**). We excluded 1,989 articles for various reasons, detailed in **Appendix C**, and included 223 publications. Of these, 26 publications reported eligible outcomes for the overarching question, KQ 1. Details of quality assessments of included studies and studies excluded because of poor quality are in **Appendix D Tables 1-11**.

Results by Key Question

Key Question 1

KQ 1a. Does screening for lung cancer with LDCT change the incidence of lung cancer and the distribution of lung cancer types and stages (i.e., stage shift)?

b. Does screening for lung cancer with LDCT change all-cause mortality, lung cancer mortality, or quality of life?
c. Does the effectiveness of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?
d. Does the effectiveness of screening for lung cancer with LDCT differ by the number or frequency of LDCT scans (e.g., annual screening for 3 years, the protocol used in the NLST, vs. other approaches)?

Summary of Included Trials

We included seven randomized, clinical trials (described in 26 articles) that evaluated lung cancer screening with LDCT (**Table 2**): NLST, Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays (DANTE), Danish Lung Cancer Screening Trial (DLCST), Italian Lung Cancer Screening Trial (ITALUNG), Lung Screening Study (LSS), the German Lung Cancer Screening Intervention Trial (LUSI), and the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) study.[32, 33, 56-79] All seven trials reported data on lung cancer incidence, lung cancer mortality, and all-cause mortality. Two trials conducted in the United States compared LDCT with CXR (LSS and NLST), and five trials conducted in Europe compared LDCT with no screening (DANTE, DLCST, ITALUNG, LUSI, and NELSON). Only the NLST (53,454 participants) and NELSON (15,792 participants) were adequately powered to assess for a lung cancer mortality benefit.[32, 76] Sample sizes ranged from 2,472 (DANTE) to 4,104 (DLCST) for the other five trials.[59, 62, 65, 69, 71] The age range for eligibility was similar across trials, with all ranges falling within 50 to 74 years of age. Current smokers ranged from 48 to 77 percent of the participants in each trial. The majority of participants were male in all trials (range, 56% to 100%); the DANTE trial enrolled 100 percent male participants and NELSON enrolled 84 percent males. The majority of participants were white in all trials; in the NLST, 91 percent were white, less than 5 percent were black, and less

than 2 percent were Hispanic or Latino. Six of the included trials evaluated annual screening, although the number of screening rounds varied, ranging from two (LSS) to five (DANTE, DLCST, and LUSI). NELSON evaluated four rounds of screening with increasing intervals for each round (baseline and after 1, 3, and 5.5 years). NELSON was also unique in using volumetric measurements of detected nodules and calculating volume-doubling time to define positive screening results (see KQ 3 for further details about definitions of positive tests for all trials).

Trials varied in their definition of a positive screen and in the followup evaluation process (see KQ 3 and KQs 4/5 section on false positives for details). All trials began enrollment between 2000 and 2007. Median duration of followup for lung cancer mortality (including publications describing long-term post-trial followup) ranged from 5.2 (LSS) to 12.3 (NLST) years. Compared with the prior systematic review conducted for the USPSTF, longer followup or more complete endpoint verification was available from DANTE,[61] DLCST,[67] LSS,[75] and the NLST,[63, 74] and three additional trials—NELSON,[76] ITALUNG,[62] and LUSI[59, 73]—reported data relevant to this KQ.

The NLST was rated as good quality for the main trial outcomes.[32, 57, 58] The extended post-trial followup of NLST was rated as fair quality because of using different ascertainment methods during trial years (with a verification committee) than for post-trial years (relying on registries and without a verification committee); lack of information on any post-trial screening with LDCT that may have taken place in either the LDCT or the CXR group; missing data for lung cancer incidence for 11 out of 33 centers (representing 12.4% of trial participants) that did not have a home state cancer registry available for linkages (this was not a concern for mortality outcomes because linkage to the National Death Index was available for all but 2.2% of trial participants); and, for estimates of overdiagnosis, risk of biasing estimates toward the null because the comparison group received CXR (rather than no screening test).

The main methodological limitations of the NELSON trial included risk of ascertainment bias and lacking details on potential harms of screening (e.g., further testing after screening, such as biopsies, and related harms). Ascertainment included a blinded review of medical files for 296 out of 426 (69.5%) of deceased Dutch patients with known lung cancer; the ascertainment therefore lacked blinded review for over 30 percent of deceased Dutch patients with known lung cancer and for over 80 percent of all 1,728 deaths that occurred. The limited blinded review revealed concordance of 86.1 percent among members of the independent expert committee and a sensitivity and specificity of 92.6 percent and 98.8 percent of the official death certificate for the study's primary outcome (lung cancer mortality). It was not reported whether the 296 blinded medical files reviewed were equally divided between the screening and control groups, raising additional concerns for differential bias in ascertainment. Methods used by the various registries for ascertainment were not reported. For females, there was limited reporting of some information, such as recruitment and selection for the study and adherence to the screening intervention.

We excluded one trial (the Multi-centric Italian Lung Detection [MILD] study) for poor quality;[80, 81] sensitivity analyses in **Appendix E** show results of that trial for lung cancer mortality and all-cause mortality. As in the prior report for the USPSTF, MILD was considered

to have a high risk of bias because of significant differences between the LDCT and no-screening groups at baseline, raising concerns about inadequate randomization, differential followup between groups (with less followup among the control group), high risk of measurement bias, and inability to reach its planned sample size (of 10,000 participants).

Incidence of Lung Cancer and Distribution of Lung Cancer Types and Stages

Overall, the cumulative incidence of lung cancer was higher in LDCT screening groups than in control groups for all studies except for the ITALUNG study (**Figure 3** and **Appendix E Table 2**. Adenocarcinomas were the most commonly diagnosed lung cancer type in both arms of all trials (ranging from 35% [NLST] to 68% [LUSI] of lung cancers diagnosed in LDCT arms) (**Appendix E Table 2**). All included trials reported more Stage I cancers in LDCT groups than in control groups (**Appendix E Table 2**). Most trials reported between 45 and 50 percent Stage I lung cancers in the LDCT groups; absolute between-group differences for Stage I lung cancers ranged from 8 (LSS) to 48 percent (LUSI). **Figure 4** shows the increases in early stage (I-II) and decreases in late stage (III-IV) lung cancer incidence, representing stage shift. At 6.5 years followup, the NLST reported a higher incidence of lung cancer among LDCT participants (4.1%; 1,089 lung cancers; 662 per 100,000 person-years) than among CXR participants (3.6%; 969 lung cancers; 558 per 100,000 person-years). The calculated incidence rate ratio was 1.12 (95% CI, 1.02 to 1.22). The LDCT and CXR groups had similar proportions of adenocarcinomas (35% vs. 34% of incident cancers), squamous cell carcinomas (22% vs. 22%), small cell carcinoma (13% vs. 16%), and other lung cancer types (**Appendix E Table 2**). For stage distribution, the trial reported more Stage I lung cancers in the LDCT group than the CXR group (520 vs. 289 Stage I lung cancers; 50% vs. 31% of incident lung cancers) and fewer Stage IV lung cancers (226 vs. 335; 22% vs. 36%, respectively). An extended followup of the NLST reported no statistically significant difference between groups for overall lung cancer incidence (1,701 lung cancers for the LDCT group vs. 1,681 for the CXR group; calculated incidence rate ratio of 1.01 [0.95, 1.08] **Figure 3**). For stage distribution after 11.3 years, the extended followup identified more Stage I lung cancers in the LDCT group than in the CXR group (40% vs. 27% of incident lung cancers) and fewer Stage IV lung cancers (28% vs. 36%, respectively) (**Appendix E Table 2**). The extended followup used linkages to state cancer registries and the National Death Index to ascertain outcomes beyond the original trial (rather than the same ascertainment methods used for the original trial).

Lung Cancer Mortality

Figure 5 shows the calculated IRRs for the trials that reported lung cancer mortality. Only the NLST and NELSON had sufficiently large sample sizes to detect a difference between groups. The original publication of the main results from the NLST reported a relative risk reduction in lung cancer mortality of 20.0 percent (95% CI, 6.8 to 26.7);[32] a subsequent publication with additional endpoint verification for lung cancer deaths (with approximately an additional year of followup covered, going to the prespecified endpoint) reported a relative reduction of 16 percent (95% CI, 5 to 25).[63] Over almost 7 years of followup, and over 140,000 person-years of followup in each group, the NLST found a significant reduction in lung cancer mortality with three rounds of annual LDCT screening compared with CXR (469 vs. 552 lung cancer deaths;[63] 280 per 100,000 person-years vs. 332 per 100,000 person-years; calculated IRR, 0.85 [95% CI, 0.75 to

0.96]). These findings indicate an NNS to prevent one lung cancer death of 323 over 6.5 years of followup. This calculated NNS is similar to the NNS reported by the initial NLST results publication (i.e., NNS 320 among those undergoing ≥1 screens; intention-to-screen analysis, NNS of 310 [95% CI, 190 to 840]) but is slightly different because of the incorporation of the additional endpoint verification. Analysis of extended followup data of NLST participants at 12.3 years after randomization found a similar absolute difference between groups (1,147 vs. 1,236 lung cancer deaths; RR, 0.92 [95% CI, 0.85 to 1.00]; absolute difference between groups of 3.3 [95% CI, -0.2 to 6.8] lung cancer deaths per 1,000 participants). The NELSON trial reported a reduction in lung cancer mortality for four rounds of screening with increasing intervals between LDCTs (at baseline, 1 year, 3 years, and 5.5 years). Combining NELSON data for males and females, there were 181 lung cancer deaths among participants in the screening group and 242 in the control group (calculated IRR, 0.75 [95% CI, 0.61 to 0.90]) over 10 years of followup. These findings indicate a NNS to prevent one lung cancer death of 130 over 10 years of followup. Results of the other trials were very imprecise and did not show statistically significant differences between screening with LDCT and no screening (**Figure 5**).

All-cause Mortality

Figure 6 shows the calculated IRRs for the trials that reported all-cause mortality. The NLST found a reduction in all-cause mortality with LDCT screening compared with CXR (1,912 vs. 2,039 deaths; 1,141 per 100,000 person-years vs. 1,225 per 100,000 person-years; calculated IRR of 0.93 [95% CI, 0.88 to 0.99]). To prevent one death from any cause, the NNS from the NLST was 219 (95% CI, 112 to 5,000). The other trials found no statistically significant differences between screening with LDCT and no screening, but results were imprecise (**Figure 6**). In the NELSON trial, there were more all-cause deaths in the LDCT screening group than in the control group (868 vs. 860), although the difference between groups was not statistically significant.

Quality of Life

None of the included trials assessed for potential benefits of LDCT screening on quality of life (some evaluated short-term quality of life to assess for possible psychosocial harms of screening, as described in KQ 4, but none evaluated quality of life over the longer course of the trial).

Subgroups

All included trials enrolled participants at high risk for lung cancer (based on age and smoking history). Seven publications using DLCST, LUSI, NELSON, or NLST data described subgroup analyses for at least one of the following; age, sex, race/ethnicity, smoking status and pack-years, history of COPD, and other pulmonary conditions.[63, 64, 66, 67, 73, 74, 76] A post hoc analysis of NLST data reported that 88 percent of the mortality benefit was achieved by screening the 60 percent of participants at highest risk for lung cancer death.[56] The 20 percent of participants at lowest risk accounted for just 1 percent of prevented lung-cancer deaths.[56] Other post hoc analyses of NLST data reported lung cancer mortality by sex (RR 0.73 for women vs. 0.92 for men, p=0.08), age (RR 0.82 for <65 vs. 0.87 for ≥65, p=0.60), race/ethnicity (hazard ratio [HR] 0.61 for black individuals vs. 0.86 for whites, p=0.29), and smoking status (RR 0.81 for current smokers vs. 0.91 for former smokers, p=0.40), and did not identify statistically significant differences

between groups.[63, 64, 66] A long-term followup of NLST participants at 12.3 years reported similar results for subgroups and did not identify statistically significant interactions by sex, age, or smoking status (sex: RR 0.86 for women vs. 0.97 for men, p=0.17; age: RR 0.86 for <65 years vs. 1.01 for ≥65 years, p=0.051; smoking status: RR 0.88 for current smokers vs. 1.01 for former smokers, p=0.12).[74] Both LUSI and NELSON reported a similar pattern for subgroups by sex as found in NLST that was not statistically significantly different between groups (LUSI: women, HR=0.31 [95% CI, 0.10 to 0.96] vs. men, HR=0.94 [95% CI, 0.54 to 1.61], p=0.09) or without reporting an interaction test (NELSON: women, RR 0.67 [95% CI, 0.38 to 1.14] vs. men, RR 0.76 [95% CI, 0.61 to 0.94] at 10 years of followup).[73, 76] NELSON reported analyses by age group among the men in the trial (not including the women in those analyses) but did not report interaction tests for subgroups defined by age (RRs ranged from 0.59 [95% CI, 0.35 to 0.98] for persons aged 65 to 69 years at randomization to 0.85 [95% CI, 0.48 to 1.50] for persons aged 50 to 54 years at randomization).[76] In a post hoc analysis of the DLSCT trial, age and having both COPD and greater than or equal to 35 pack-years of smoking were associated with an increased risk of death from lung cancer.[67]

Difference in Effectiveness by the Number or Frequency of LDCT Scans

Only the MILD study, which was excluded for poor quality, had a direct comparison by frequencies, comparing annual screening, biennial screening, and no screening.[82] No good- or fair-quality studies directly compared number or frequency of LDCT scans. Screening intervals were similar for all trials except for NELSON (which used increasing intervals between tests for each of its four screening rounds), with screening done annually. The number of screening rounds varied across studies; the NLST had three annual scans. Reported participation rates across studies varied somewhat but were 90 percent or greater for all studies except for ITALUNG (adherence to screening of 81% across all rounds of screening) and LSS (77% at year 1 among participants with positive baseline screen).

Key Question 2. Does the Use of Risk Prediction Models for Identifying Adults at Higher Risk of Lung Cancer Mortality Improve the Balance of Benefits and Harms of Screening Compared With the Use of Trial Eligibility Criteria (e.g., NLST Criteria) or the 2013 USPSTF Recommendations?

Summary

For benefits, four studies of three different risk prediction models (a modified version of a model developed from participants of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial [PLCOm2012], the Lung Cancer Death Risk Assessment Tool [LCDRAT], and Kovalchik model) estimating outcomes in four different cohorts reported increased screen-preventable deaths compared with the risk factor–based criteria used by the NLST or USPSTF (in the 2013 recommendations). Three studies demonstrated improved screening efficiency (determined by the NNS) of risk prediction models compared with risk factor–based screening, while one study showed mixed results. For harms, eight studies of 13 different risk prediction models (PLCOm2012, simplified PLCOm2012, Bach, Liverpool Lung Project [LLP], simplified LLP,

Knoke, Two-Stage Clonal Expansion [TSCE] incidence, TSCE Cancer Prevention Study [CPS] death, TSCE Nurses' Health Study [NHS]/Health Professionals Followup Study [HPFS] death), the Hunt Lung Cancer model, LCDRAT, COPD-LUCSS, Kovalchik model) estimating outcomes in four different cohorts reported similar numbers of false-positive selections from risk prediction with respect to lung cancer events (i.e., the risk prediction model selected people to be screened who did not have or develop lung cancer or death from lung cancer) and mixed findings for rates of false-positive selections with respect to lung cancer events when comparing risk prediction models with the risk factor–based criteria used by the NLST or USPSTF. In general, estimates of benefits and harms were consistent but imprecise, primarily because of a lack of an established risk threshold to apply the model.

Description of Included Studies

Nine good- or fair-quality studies were included, which evaluated 13 different risk prediction models.[56, 83-88] **Table 3** summarizes the predictors included in each model. The PLCOm2012 model was the most commonly evaluated model compared with risk factor–based criteria in five studies;[83, 85-87, 89] the LCDRAT model was evaluated by two studies;[84, 89] the other models were evaluated by one study each. Risk models included personal history, smoking history, family history of cancer, occupational exposures like asbestos, and lung conditions (e.g., COPD, emphysema).

The PLCOm2012 model was developed in ever-smokers in the PLCO control arm. Compared with USPSTF criteria, the PLCOm2012 model includes more personal factors (e.g., history of malignancy), more detailed smoking history, family history, and a personal history of COPD.[85] The Lung Cancer Risk Assessment Tool (LCRAT) and LCDRAT are risk models developed and validated in the control and CXR arms of the PLCO, respectively.[84] Additional eligible models for this systematic review included the Kovalchik model, the Bach model, the LLP model, simplified LLP model, the Knoke model, the Hunt Lung Cancer model, and three TSCE models predicting lung cancer incidence and death. Models included a variety of additional risk factors, such as smoking intensity (cigarettes per day);[56, 84, 85, 90, 91] occupational asbestos exposure;[90, 92] lung conditions of emphysema, COPD, and pneumonia;[56, 84, 85, 88, 92] and family history of lung cancer.[56, 84, 85, 92]

The models included in the evidence review were developed across several cohorts: smokers in the PLCO control arm,[84, 85] NLST control arm,[56] the Pittsburg Lung Screening Study,[88] the Carotene and Retinol Efficacy Trial,[90] the Liverpool Lung Project case-control study,[92] the NHS, HPFS,[93] the American Cancer Society's first Cancer Prevention Study (CPS-I), the American Cancer Society's second Cancer Prevention Study (CPS-II),[94] and the HUNT study.[95] The models were externally validated in four cohorts in the United States,[56, 83-85] one in Spain,[88] one in Norway,[95] and one in Australia.[86] Specifically, these cohorts included the NLST control (CXR) arm or pooled arms,[84, 85] smokers from the CXR and control arms of the PLCO Screening Trial 2003-2009,[56, 83-85] the NHIS 2010-2012,[84] NHIS 2015,[89] the Australian 45 and Up Study (cohort of 267,017 Medicare-eligible individuals 2006-2009),[86] the CONOR database in Norway,[95] and the Pamplona-International Early Lung Cancer Detection Program (572 individuals 2001-2013).[88] Models predicted lung cancer incidence,[85] lung cancer death,[56, 94, 96] or both.[90] The time horizon of the predictions was 1 year for the Bach model and TSCE models,[90,

[93, 94] although to obtain predictions for longer time frames, investigators repeated the risk prediction for multiple years: 5 years for the LLP model,[92] the Katki model (LCDRAT and LCRAT),[84] and the Kovalchik model;[56] 6 years for the PLCOm2012 model, the HUNT model,[95] and the Knoke model;[96] or were not reported.[88]

Outcomes were estimated by applying each risk model to the cohort (or cohorts) used for external validation. There are currently no consensus risk thresholds to deploy risk prediction models for lung cancer screening. In other words, there is not a particular 5- or 6-year calculated risk for lung cancer incidence or lung cancer death that is agreed upon as the threshold for recommending screening. Individual study investigators employed one or more of the following strategies to determine a risk threshold, which could be used to estimate benefit or harm outcomes of using a risk-based approach to screening compared with NLST or USPSTF criteria:

1. Fixed-USPSTF (or NLST) population size: select model risk threshold such that the number screened matches the number of USPSTF (or NLST) screen-eligible smokers in the United States[83-87]
2. Fixed-USPSTF effectiveness estimate: select model risk threshold such that the NNS matches the NNS of USPSTF-eligible smokers in the United States[84]
3. Stratification by risk quantiles or quintiles[56, 95]
4. Comparable or improved mortality compared with the NLST: select risk threshold at which lung cancer mortality rates were consistently lower in the CT arm vs. CXR arm of the NLST[86, 87]
5. Optimal classification based on receiver operator curve[86]
6. Risk threshold ≥2% absolute risk[86]

Twelve models demonstrated fair to good discrimination for both lung cancer incidence and lung cancer mortality. Area under the curve [AUC] ranged from 0.62 to 0.89 for eligible studies with better discrimination for lung cancer mortality than for lung cancer incidence and better discrimination in PLCO cohorts compared with the NLST or other cohorts (**Table 3**). For lung cancer mortality, the Katki model, Kovalchik model, PLCOm2012 model (full and simplified), and Bach models generally had better discrimination (and satisfactory calibration) than the other risk prediction models.[56, 83-86] For one model (COPD-Lung Cancer Screening Score [LUCSS]), the included study did not report discrimination or calibration.[88] Studies reporting discrimination or calibration for these models that did not also report eligible KQ 2 outcomes are not included in this summary.

Results of Included Studies

Studies of the PLCOm2012 Model, the Most Commonly Evaluated Model

Five studies evaluated the PLCOm2012 model using five different risk thresholds estimating outcomes over 6 years (**Table 4**).[83, 85-87, 89] Additionally, a simplified version of the PLCOm2012 model was evaluated that included age, and smoking history only.[83]

Two studies of the PLCOm2012 model calculated an increase in screen-prevented lung cancer deaths compared with the NLST criteria over 6 years using assumptions of NLST-like reduction in lung cancer mortality (20%) among smokers in the CXR arm of the PLCO.[85, 89] These two

studies also evaluated NNS to prevent one lung cancer death. One study found a reduction in NNS to prevent one lung cancer death (174 vs. 203).[85] The other study evaluated three risk thresholds (1.3%, 1.51%, and 2.19%) with NNS decreasing as the risk threshold increased (222, 207, and 169) such that the NNS was higher when using a risk prediction model for the two lowest risk thresholds compared with risk factor–based screening.[89]

Across studies of the PLCOm2012 model using a fixed-population approach to setting a risk threshold, there were a similar percentage of false-positive selections for screening and similar rates of false-positive selections for screening with respect to lung cancer deaths when compared with the USPSTF or NLST criteria (range 96.0 to 97.9%, and 37.1 to 38.1 rates, respectively). In the 45 and Up Study, the rate of false-positive selections for screening with respect to lung cancer incidence was lower compared with PLCO cohorts, but similar to false-positive rates for the risk prediction model and risk factor–based screening criteria. Additionally, a simplified version of the PLCOm2012 model including age, and smoking history only was evaluated using fixed-NLST population risk thresholds (1.19% to 1.20%) and similarly found no difference between number of false positive selections for screening or rates of false-positive selections for screening with respect to lung cancer incidence or death when compared with the NLST criteria.[83]

Using the risk threshold of at least 2 percent yielded a lower number of false-positive selections for screening and rates of false-positive selections for screening with respect to lung cancer incidence compared with USPSTF criteria in one study[86] and a lower number of false-positive selections per prevented deaths in another.[89] Studies using a risk threshold based on or close to the NLST mortality benefit (1.51%, 1.49% for optimal receiver operating characteristic curve classification) generally had similar numbers of false-positive selections, but mixed results with respect to rates of false-positive selections, depending on the cohort that was used to estimate outcomes. Two studies applied the PLCOm2012 model to cohorts of ever-smokers where the risk prediction model yielded mixed rates of false-positive selections with respect to lung cancer incidence compared with risk factor–based criteria: in the PLCO-CXR cohort, 33.8 (risk threshold ≥ 1.51%) vs. 37.3 (USPSTF criteria) and the 45 and Up Study, 28.0 for risk threshold ≥ 1.51 percent, 28.2 for risk threshold ≥ 1.49 percent, 23.7 for USPSTF criteria.[86, 87] Neither of these two studies evaluated the effect of risk prediction models on screen-prevented lung cancer deaths or NNS.

Studies of Risk Prediction Models Reporting Benefits and Harms

For the **LCRAT and LCDRAT**, fixed-USPSTF-population, fixed-USPSTF effectiveness strategies, and comparable mortality benefit to NLST were used to select risk thresholds to apply the model to the NHIS 2010-2012 and NHIS 2015.[84, 89] Study investigators assumed NLST-like increases in lung cancer incidence and 20 percent reduction in lung cancer mortality to estimate screen-preventable deaths, NNS, false-positive selections per prevented death (also called "screening efficiency"), and overdiagnosed lung cancer per prevented death. **Kovalchik et al** developed a risk model predicting lung cancer death in the NLST control arm and applied the model to the NLST-CT arm to estimate the outcomes above.[56] Several risk thresholds were evaluated in Kovalchik et al based on risk quintiles; results for quintiles 3-5 and 4-5 corresponding to risk thresholds of 0.84 percent and 1.23 percent are shown in **Table 5**.[56]

Studies of the **PLCOm2012 model and LCDRAT model** estimated a greater number of screen-preventable lung cancer deaths than with the NLST criteria. Calculations for some studies yielded a much higher total number of estimated screen-preventable lung cancer deaths because larger national samples of smokers were used (size of sample greater than 9 million) compared with the samples used to estimate outcomes for the other models (i.e., PLCO and NLST trial arms that included ~20,000-30,000 persons).[84, 89] Kovalchik et al reported outcomes for high-risk subsets of the NLST CT screening arm, so screen-preventable lung cancer deaths were intrinsically smaller for the subset compared with the whole trial arm.

Most studies of the three risk prediction models estimated a lower NNS than screening with the NLST criteria, ranging from 29 to 136 fewer subjects screened per lung cancer death prevented. Exceptions included a study of the LCDRAT that used the PLCO-fixed effectiveness threshold, which intentionally sets the NNS equal to that achieved by the NLST criteria,[84] and one study that used a fixed-population risk threshold (1.3%) and NLST-like mortality benefit threshold (1.51%) in a more modern cohort (NHIS 2015) in which NNS was higher using the risk prediction model compared with risk factor−based criteria (222 and 207, respectively, vs. 194).[89]

Screening efficiency also improved in most cases when a risk-based approach was applied compared with the NLST criteria (range of false-positive selections per prevented lung cancer death: 64-167 for risk models vs. 108-196 for the NLST criteria). The exception was application of the PLCOm2012 model to the 2015 NHIS cohort in which risk thresholds of 1.35 percent and 1.51 percent were used; false-positive selections per prevented deaths ranged from 207 to 222 compared with 194 for USPSTF criteria.[89] For the two thresholds of LCDRAT evaluated, overdiagnosis was similar for risk-based screening and screening using the NLST criteria.

Other Studies of Risk Prediction Models Reporting Only Harms

For the remaining models included in the systematic review—the **Bach**, **LLP**, **simplified LLP**, **Knoke**, **TSCE model, HUNT Lung Cancer Model,** estimates of false-positive selections and rates of false-positive selections with respect to lung cancer incidence or death were compared with the NLST criteria using PLCO cohorts (fixed-NLST population-based risk threshold).[83, 95] In general, false-positive percentages and rates using risk-based screening were similar to screening using the NLST criteria (range of false-positive selections 97 to 98%; range of rates of false-positive selections 21 to 38%).

The **COPD-LUCSS score** predicts lung cancer incidence in subjects with COPD, including risk factors of age, body mass index, smoking in pack-years, and radiologic emphysema.[88] Using a risk threshold of COPD-LUCSS score of 7 to 10, this score had a lower number of false-positive selections for screening with respect to lung cancer incidence than the NLST criteria (86% vs. 91%).

Key Question 3. Accuracy

a. What is the accuracy of screening for lung cancer with LDCT?
b. Does the accuracy of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?
c. Does the accuracy of screening for lung cancer with LDCT differ for various approaches to nodule classification (i.e., those based on nodule size and characteristics)?

Summary

Fifty-three articles were eligible for this KQ.[32, 33, 38, 57-61, 64, 70, 71, 76-79, 82, 97-132] Of those, many reported information from the same study (i.e., redundant data), incomplete data, or preliminary data that were later updated in another publication. Therefore, we focused on the results from the 24 publications with the most complete data.[59, 61, 64, 76, 82, 97, 99-101, 103, 104, 107, 108, 111, 113, 115, 119, 121-123, 126, 127, 130, 131] Sensitivity of LDCT from 13 studies (76,856 total participants) ranged from 59 to 100 percent; all but three studies reported sensitivity over 80 percent. Specificity of LDCT from 13 studies (75,819 total participants) ranged from 26.4 to 99.7 percent; all but three reported specificity over 75 percent. Positive predictive value (14 studies, 77,840 participants) ranged from 3.3 to 43.5 percent. Negative predictive value (9 studies, 47,496 participants) ranged from 97.7 to 100 percent. Variability in accuracy was mainly attributed to heterogeneity of eligibility criteria, heterogeneity of screening protocols (e.g., number of screening rounds, screening intervals), heterogeneity and completeness of followup length (e.g., to identify false-negative screens), and heterogeneity in the definitions (e.g., of positive tests, indeterminate tests, false-positive test, false-negative tests). Three studies (2,211 observations) reported on reliability, finding fair to moderate reliability among radiologists.[103, 108, 113] Regarding subgroups, one study demonstrated that LDCT had higher sensitivity and lower specificity for persons 65 or older than for younger persons.[64] Three studies (73,404 participants) compared various approaches to nodule classification (Lung-RADS or I-ELCAP) using the NLST protocol as the basis for comparison.[100, 104, 107] These demonstrated that using Lung-RADS in the NLST would have increased specificity while decreasing sensitivity, and that increases in positive predictive value (PPV) are seen with increasing nodule size thresholds.

Detailed Results: Accuracy

RCTs and nonrandomized studies that reported on sensitivity, specificity, or predictive values (or provided the data that allowed us to calculate measures of accuracy) are summarized in **Tables 6** and **7**, respectively. Six RCTs[59, 61, 76, 82, 99, 101] and seven nonrandomized studies[115, 121, 123, 126, 127, 130, 131] provided sensitivity data. Sensitivity in the RCTs ranged from 59 to 95 percent. Sensitivity in the nonrandomized studies ranged from 87.7 to 100 percent, with five of the nonrandomized studies having sensitivity greater than 90 percent. Six RCTs[59, 61, 76, 82, 99, 101] and seven nonrandomized studies[111, 121, 123, 126, 127, 130, 131] provided specificity data. Specificity in the RCTs ranged from 26.4 to 99.2 percent, and specificity in the nonrandomized studies ranged from 34.0 to 99.7 percent. All but two of the nonrandomized studies[111, 130] had specificity greater than 90 percent. Nine RCTs[59, 61, 76, 82, 99, 101, 119, 122] and five nonrandomized studies[107, 111, 123, 130, 131] provided PPV data. PPV ranged from 3.3 to 43.5 percent in the RCTs and from 3.5 to 20.9

percent in the nonrandomized studies. Six RCTs[59, 61, 76, 82, 99, 101] and three nonrandomized studies[123, 130, 131] provided negative predictive value (NPV) data. NPV ranged from 97.7 to 99.9 percent in the RCTs and from 99.2 to 100 percent in the nonrandomized studies.

Among the trials that reported a reduction in lung cancer mortality, NLST and NELSON, the reported sensitivities were 93.1 and 59 percent and reported specificities were 76.5 and 95.8 percent, respectively.[76, 101] Although the NPVs were similar for the NLST and NELSON (99.9% and 97.7%, respectively), the PPVs were vastly different (3.3% and 43.5%, respectively). This difference could potentially be accounted for by the difference in screening protocols—NELSON used a volumetric approach and provided for an indeterminate nodule result category and the NLST used an approach of maximum diameter without an indeterminate category—or possibly by the prevalence of lung cancer in each of the trial settings. Alternatively, these data could represent two different positions on the same ROC curve, illustrative of tradeoffs between sensitivity and specificity.

Numerous factors may account for the variability in accuracy across studies. There was heterogeneity in the screening protocols, particularly for the number of screening LDCT scans performed, the interval between screening rounds, and threshold for a positive test. The studies also varied in terms of their followup lengths, and some had incomplete followup data. For instance, most of the nonrandomized studies did not report the length of followup after the last screening scan. As a result of differential and incomplete followup data, some studies may not have adequately captured false-positive and false-negative screens, perhaps because of an inability to ascertain complete data on the workup of screen-positive nodules or the development of interval cancers after a negative screen. As well, the definitions for positive test, indeterminate test, false-positive test, and false-negative test varied across studies. The three most common methods for defining a positive test were similar to those used by the NLST (NCN ≥4-mm maximum diameter), I-ELCAP (NCN ≥5-mm average of maximum length and width, later changed to 6 mm), or NELSON protocols (e.g., volume of NCN ≥500 mm^3).

Reliability

Three studies (2,211 observations) conducted analyses of RCT data to report reliability outcomes, finding fair to moderate reliability among radiologists.[103, 108, 113] Two of these studies calculated kappa values among radiologists; all average outcomes either had fair (kappa 0.21 to 0.40) or moderate (kappa 0.41 to 0.60) agreement levels. One study using data from three NELSON trial sites evaluated agreement among radiologists for a set of 160 nodules equally distributed across solid, part-solid with large solid component, part-solid with small solid component, and ground glass nodule definitions, finding moderate agreement (kappa 0.51 [95% CI, 0.30 to 0.68]).[113] Another study using 1990 scans from the DLCST focused on identifying emphysema (and other outcomes not eligible for this review) but also reported some outcomes eligible for this review. Specifically, it reported moderate agreement in identifying pleural nodules (kappa 0.53), centrilobular nodules (kappa 0.41), and masses (kappa 0.42), with fair agreement for subpleural/paraseptal nodules (kappa 0.24).[108] Finally, a study of data from the NELSON trial found that 22 of the 61 interval or post-screen cancers diagnosed in NELSON were, in retrospect, visible on the prior LDCT.[103] It was determined that 20 of these 22 were

detection errors (i.e., the radiologic abnormality was not detected), and the other two were detected but were misinterpreted. The study did not report kappa statistics.

Variation by Subgroups

Two studies (44,792 participants) assessed how the accuracy of LDCT varied by subgroups.[64, 126] An analysis of NLST data stratified by age of Medicare eligibility (age ≥65) demonstrated increased sensitivity (94.3% vs. 93.2%), decreased specificity (72.3% vs. 78.0%), and increased PPV (4.9% vs. 3.0%, $p < 0.001$) for Medicare-eligible participants. The increased PPV was attributed to higher cancer prevalence in this population.[64] Data from the Osaka Cancer Registry Database were stratified by sex and smoking status, finding no statistically significant differences between women and men for sensitivity (84.6% [95% CI, 65.0 to 100] vs. 90.6% [95% CI, 80.5 to 100]) or specificity (93.5% [95% CI, 92.6 to 94.4] vs. 92.1% [95% CI, 91.3 to 92.9]) or by smoking status for sensitivity (current 84.0% [95% CI, 69.6 to 98.4], former 85.7% [95% CI, 59.8 to 100], nonsmoker 100% [95% CI, NR]), or specificity (current 92.4% [95% CI, 91.6 to 93.3], former 91.5% [95% CI, 89.9 to 93.1], nonsmoker 93.5% [95% CI, 92.5 to 94.4]).[126]

Variation by Approaches to Nodule Classification

Three retrospective studies compared how various approaches to nodule classification would alter the accuracy of LDCT.[100, 104, 107] The first study (26,722 participants) was a retrospective analysis that applied Lung-RADS criteria to NLST data and found that using Lung-RADS (with Lung-RADS categories 1 and 2 considered negative results) was estimated to increase the specificity of LDCT (from 73.4% to 87.2% at baseline, $p<0.001$; from 78.2% to 94.7% after baseline, $p<0.001$) but decrease the sensitivity (from 93.5% to 84.9% at baseline, $p<0.001$; from 93.8% to 78.6% after baseline, $p<0.001$) compared with using the NLST criteria.[100] The second study (5,848 NLST participants with positive LDCT screens) evaluated how using I-ELCAP criteria and other thresholds for a positive test (e.g., 5-mm average diameter, 6 mm, etc.) alters the frequency of positive results and related outcomes compared with the NLST criteria (4-mm longest diameter).[104] The study did not report measures of accuracy, but the data reported allow for calculation of PPV and show that using a 5-mm average diameter criterion (applied to NLST data) increases the PPV (from 4% to 5.7%), as does increasing the threshold further (e.g., PPV 8.5% for 6 mm, PPV 12.2% for 7 mm). However, this analysis did not calculate other test characteristics (sensitivity, specificity, NPV) and excluded 848 nonsolid noncalcified nodules that would have otherwise met the criteria for a positive screen.[104] Similarly, the third study estimated that PPV would increase with increasing thresholds for defining a positive result (from 5-mm to 6-mm average diameter).[107]

Comparing volumetric and nonvolumetric (i.e., maximum diameter or average maximum length and width) approaches indicates that the PPV in trials using volumetric approaches to nodule classification tends to be higher than in those using nonvolumetric approaches. However, because there are no direct comparisons of these approaches, differences in study populations (e.g., lung cancer incidence) and other contributors to heterogeneity across studies may account for the differences in PPV. The NPVs are universally high using both approaches, and no trends in sensitivities or specificities are apparent.

Key Questions 4 and 5. Harms of Screening, Workup, or Surveillance

KQ 4a. What are the harms associated with screening for lung cancer with LDCT?
- b. Do the harms of screening for lung cancer with LDCT differ with the use of Lung-RADS, I-ELCAP, or similar approaches (e.g., to reduce false-positive results)?
- c. Do the harms of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?

KQ 5a. What are the harms associated with workup or surveillance of nodules?
- b. Do the harms of workup or surveillance of nodules differ with the use of Lung-RADS, I-ELCAP, or similar approaches (e.g., to reduce false-positive results)?
- c. Do the harms of workup or surveillance of nodules differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?

Radiation Exposure

Nine publications reported on radiation associated with LDCT (**Table 8**).[32, 67, 111, 117, 124, 130, 133-135] Most of those reported the radiation associated with one LDCT, with ranges from 0.65 mSv to 2.36 mSv. Two of the studies evaluated the cumulative radiation exposure for participants undergoing screening with LDCT.[134, 136] Using the results of those two studies to estimate the cumulative radiation exposure for 25 years of annual screening (i.e., annual screening from age 55 to 80 as recommended by the USPSTF in 2013) yields 20.8 mSv to 32.5 mSv.

One of the two studies describing cumulative exposure reported that screened participants in the ITALUNG trial had cumulative radiation exposure of 3.3 mSv for multidetector CT (MDCT).[136] The authors estimated this would result in a lifetime risk of fatal cancer of 0.11 per 1,000 subjects for MDCT after the four screening rounds.

The other evaluated the Continuing Observation of Smoking Subjects (COSMOS) study and reported a cumulative radiation dose from LDCT and positron emission tomography (PET) CT scans (individual PET CTs had a median radiation dose 4.0 mSv) to be 13.0 mSv for women and 9.3 mSv for men after 10 years of annual screening.[134] This study also noted cumulative dosing by interval years and sex, with men averaging 3.0 mSv (range 1.9 to 27.4) after 3 years and 5.2 mSv (range 2.9 to 39.6) after 5 years and women averaging 4.2 mSv (range 2.9 to 23.3) after 3 years and 7.2 mSv (range 4.1 to 26.8) after 5 years (p values for comparison by sex not reported). This study additionally estimated lifetime attributable risk of cancer estimated with the National Research Council's Biological Effects of Ionizing Radiation VII report, which estimated the lifetime attributable risk of cancer incidence after radiation exposure for specific organs. Using this report, the estimated lifetime risk of cancer from radiation of 10 annual LDCTs was 2.6 to 8.1 major cancers per 10,000 people screened (converting to every 1,000 people screened: 0.26 to 0.81 major cancers). The study reported that men and women starting at an earlier age (50-54 years old) will have a higher number of radiation-induced major cancers (males 3.7 and females 8.1 cancers per 10,000 screened) than older (≥65 years old) participants (males 2.6 and females 5.1 cancers per 10,000 screened); no statistical testing for differences was reported. Projected risk specifically for radiation-induced lung cancer was similar, with younger patients (beginning at ages 50-54) having a higher risk than those beginning screening at age 65 years or older

(males 2.1 and females 5.5 cancers per 10,000 screened vs. 1.4 and 3.8 cancers per 10,000 screened for those 65 years or older, respectively). The authors estimated that there will be one major radiation-induced cancer (lung, stomach, colon, liver, bladder, thyroid, breast, ovaries, uterus, or leukemia) for approximately every 100 lung cancers detected by screening during the 10 years of the study.

None of the included studies provided estimates for the lifetime risk of radiation-induced cancers or fatal cancers from continuing annual screening up to age 80.

False-Positive Results and Followup Evaluations

Twenty seven publications reported false-positive rates or enough information to determine the rate of false positives, defined as any result leading to additional evaluation (repeat LDCT scan prior to next annual screening, PET scan, biopsy, etc.) that did not result in a diagnosis of cancer.[32, 38, 57-59, 64, 65, 69, 70, 76, 82, 102, 104, 107, 111, 117, 120-123, 128, 130-132, 137-139] False-positive rates varied widely across studies, most likely due to differences in definitions of positive results, such as cut-offs for nodule size (e.g., 4 mm vs. 5 mm vs. 6 mm), use of volume doubling time, and various nodule characteristics considered. We determined the false-positive rate by dividing the number of false positives by the number of individuals screened with LDCT. The range of false-positive rates overall was 7.9 to 49.3 percent for baseline screening and 0.6 to 28.6 percent for individual incidence screening rounds, although rates for some subgroups were higher (e.g., age ≥65 years) (**Table 9**). For trials, rates ranged from 7.9 to 26.9 percent for baseline screening and 0.6 to 27.2 percent for incidence screening.[32, 57, 59, 64, 76, 117, 120, 122] For cohort studies, false-positive rates ranged from 9.6 to 49.3 percent for baseline screening and 5.0% to 28.6 percent for incident screening.[38, 82, 107, 121, 128, 130, 131, 137] False-positive rates generally declined with each screening round.[64, 82, 120, 121, 128, 131]

Among the trials that found lung cancer screening mortality benefit and cohort studies based in the United States, false-positive rates were 9.6 percent to 28.9 percent for baseline and 5.0 percent to 28.6 percent for incident rounds. The NLST reported false-positive rates for baseline, year 1, and year 2 of 26.3, 27.2, and 15.9 percent, respectively.[32] The NELSON trial noted false-positive rates of 19.8 percent at baseline, 7.1 percent at year 1, 9.0 percent for males at year 3, and 3.9 percent for males at year 5.5 of screening.[76, 120] One study of 112 radiologists from 32 screening centers who each interpreted 100 or more NLST scans reported a mean false-positive rate of 28.7 percent (standard deviation 13.7, range 3.8% to 69.0%).[102] Mean rates were similar for academic (25 centers) and nonacademic (7 centers) centers (27.9% vs. 26.7%, respectively).[102] An implementation study through the Veterans Administration revealed a false-positive rate of 28.9 percent of veterans eligible for screening (58% of those who were actually screened) at baseline screening.[38] False-positive rates varied across eight study sites, ranging from 12.6 to 45.8 percent of veterans eligible for screening.[38]

Regarding whether harms of screening differ with the use of Lung-RADS, I-ELCAP, or similar approaches (KQs 4b and 5b), we found no eligible studies that directly compared Lung-RADS vs. I-ELCAP within a common set of participants. Three studies assessed how use of Lung-RADS would have affected false-positive result rates.[100, 132, 139] One found a false-positive rate among baseline results for Lung-RADS of 12.8 percent (95% CI, 12.4% to 13.2%) vs. 26.6

percent (95% CI, 26.1% to 27.1%) for the NLST approach. Another study used NLST baseline data to evaluate whether Lung-RADS category 4X improves prediction of malignancy in subsolid nodules.[132] It reported false-positive rates (i.e., upgrade of a benign nodule to category 4X) for nodules in category 3 of 7 percent (95% CI, 5% to 9%), category 4A of 7 percent (95% CI, 4% to 10%), and category 4B of 19 percent (95% CI, 13% to 24%).[132] The third stratified NLST participants by risk (using the Tammemagi lung cancer risk prediction model) and found increasing false-positive rates for increasing risk, ranging from 8.3 to 17.6 percent for baseline rates and 12.9 to 25.9 percent for cumulative rates.[139] Among studies using I-ELCAP criteria, the false-positive rate ranged from 9.6 to 16.6 percent for baseline screening to 5.0 to 28.6 percent for incident screening.[121, 128, 131]

For subgroups, one study evaluating NLST data on two annual rounds of LDCT scans found a cumulative risk of at least one false-positive test to be 33 percent.[119] It reported that after a second round of screening, smokers with more pack-years had 1.5 times the odds of a false-positive result (OR, 1.53 [95% CI, 1.08 to 2.18]). Another subgroup analysis of the NLST data found higher false-positive rates in those older than 65 years (23.5% for all participants; 22.0% vs. 27.7% for those <65 years vs. ≥65 years for all rounds, p=0.001).[64]

False-Positive Evaluations

The most detrimental harms of false-positive results occur in the workup of these nodules, which can include further imaging (LDCT, CT, or PET), biopsy, or surgical procedures. Fourteen studies reported on the evaluation of false-positive results.[32, 57, 60, 64, 99, 117-119, 121, 127, 130, 133, 135, 140] Definitions of procedures and groupings of procedures varied among studies. Among all patients screened, the percentage who had a needle biopsy for a false-positive result ranged from 0.09 to 0.56 percent (**Table 10**). Complication rates from needle biopsy for false positives ranged from 0.03 to 0.07 percent of all those screened. Surgical procedures (and surgical resections) for false positives were reported in 0.5 to 1.3 percent (0.1% to 0.5%) of all screened participants.

In the NLST, false-positive results led to invasive procedures (needle biopsy, thoracotomy, thoracoscopy, mediastinoscopy, and bronchoscopy) in 1.7 percent of those screened. Complications occurred in 0.1 percent of those screened, with major, intermediate, and minor complications occurring in 0.03 percent, 0.05 percent, and 0.01 percent, respectively, of those screened. Death in the 60 days following the most invasive procedure performed occurred in 0.007 percent of those screened.[32]

No studies directly compared the workup of nodules identified by I-ELCAP or Lung-RADS, but rates of biopsy for false positives ranged from 0.09 to 0.42 percent of all persons screened in I-ELCAP studies.[118, 121] The one study using Lung-RADS found a rate for surgical procedures (e.g., mediastinoscopy, video-assisted thoracoscopic [VATS], or thoracotomy) of 0.3 percent for false positives among all those screened.[133] An evaluation using NLST data estimated that 117 invasive procedures for false positives (23.4% of all invasive procedures for false positives from the NLST) would be prevented by using Lung-RADS criteria (preventing an invasive procedure for a false positive screening result for 0.44% of all persons screened).[100]

For subgroups, a study using the NLST data evaluating age differences for invasive procedures after false positives reported a rate of 3.3 percent of all LDCT screens for those 65 years or older and 2.7 percent of all LDCT screens in those younger than 65 (p=0.039).[64]

Overdiagnosis

Five studies specifically examined overdiagnosis,[135, 141-144] and we examined seven trials for differences in cancer incidence between LDCT and comparison groups.[32, 62, 70, 72, 76, 80, 145] Overdiagnosis is the detection of a cancer in a patient that would not have become clinically apparent in the patient's lifetime. In addition to the psychological consequences of being diagnosed with cancer, the major harm of this detection is unnecessary treatment (e.g., chemotherapy, radiation, and/or surgical resection) of something that would never have caused a problem. The presence of overdiagnosis is supported by multiple trials demonstrating an excess of early-stage cancers in the screening group without eventual catch-up of cancer cases in the comparison group in the followup period.[32, 70, 72, 80, 145] In the initial publication of NLST results, there were an excess of 119 lung cancers after three screening rounds and 6.5 years of followup (total cancers: 1,060 from the LDCT group and 941 from the CXR group).[32] The post-trial followup of NLST reported that there was no significant overall increase in lung cancer incidence at a median of 11.3 years of followup (1,701 vs. 1,681, respectively, RR, 1.01 [95% CI, 0.95 to 1.09]).[74] However, the extended post-trial followup of NLST had some important methodologic limitations for ascertaining lung cancer incidence and overdiagnosis. These included using different methods during trial years (with a verification committee) than for post-trial years (relying on registries and without a verification committee); lack of information on any post-trial screening with LDCT that may have taken place in either the LDCT or the CXR group; missing data for lung cancer incidence for 11 out of 33 centers (representing 12.4% of trial participants) that did not have a home state cancer registry available for linkages; and risk of biasing overdiagnosis estimates toward the null because the comparison group received CXR (rather than no screening test). In the NELSON trial, there were an excess of 40 lung cancers after 10 years of followup since randomization, the a priori planned followup duration (total cancers 648: 344 from LDCT group and 304 from the control group; after 11 years of followup there was an excess of 14 cancers).[76] The ITALUNG trial reported a catch-up of lung cancers in the 5 years following the end of five rounds of annual screening.[62] However, inadequate duration of followup and heterogeneity of followup duration across trials limit the evaluation of overdiagnosis.

Determining the rate of overdiagnosis in screening is challenging because calculations of excess cancers are influenced by followup periods. One modeling study using the NLST data, limited by 6.5 years of followup, reported a probability of 18.5 percent (95% CI, 5.4% to 30.6%) that any detected lung cancer by screening is overdiagnosis (for NSCLC specifically, probability 22.5% [95% CI, 9.7% to 34.3%]).[142] The study reported 1.38 cases of overdiagnosis in every 320 patients needed to screen to prevent one death from lung cancer. This study additionally modeled risk of overdiagnosis with lifetime followup after five annual screens, finding an overdiagnosis rate of 12 percent (95% CI, 7% to 15%) for all NSCLC after five annual LDCT scans with lifetime followup compared with no screening. A study using data from DLCST revealed an excess of 43 cancers (96 cancers overall and 64 screen-detected in the LDCT group vs. 53 in control group) after five annual LDCT scans and 5 years of followup, placing the estimate of

overdiagnosis at 67.2 percent (95% CI, 37.1% to 95.4%) (absolute difference of cancers divided by screen-detected cancers).[141]

One study sought to determine characteristics of potential overdiagnosis cases by evaluating volume doubling time (VDT),[135] finding about 25% of cancers are slow growing or indolent. The authors acknowledge, however, that it has also been reported that previously stable nodules can increase their rate of growth rapidly.[146] A review of the Pittsburgh Lung Screening Study (PLuSS) trial cancer cases found 17/93 (18.5%) of prevalent cancers were indolent using a cut-off VDT of >400 days and a standardized uptake value of ≤1 on the PET scan.[143] Sixteen out of the 17 (94.1%) were histologically adenocarcinomas, representing potential histologic shift.

To better determine populations at greater risk of overdiagnosis, one study evaluated overdiagnosis by COPD status in a subgroup of the NLST and found an excess of 26 adenocarcinoma-associated cancers in the COPD absent group. The authors argue that an excess of this histologic group, which is predominantly early stage, may represent a histologic shift to more indolent cancers identified by screening and not a clinically significant stage shift.[144]

Smoking Behavior

One RCT (DLCST, 4,075 participants) reported in two publications, three publications reporting on studies of participants from RCTs (NELSON, NLST, LSS, 19,426 total participants), and three cohort studies (ELCAP, Mayo Lung Project, and PLuSS, 5,537 total participants) included an evaluation of the impact of LDCT screening or screening results on smoking cessation and relapse. Evidence comparing LDCT vs. controls (no screening or CXR, depending on study) for smoking cessation or abstinence outcomes does not indicate that screening leads to false reassurance. Abnormal or indeterminate screening test results may increase cessation and continued abstinence, but normal screening test results had no influence. Regarding smoking intensity, evidence was minimal, and no study showed any influence of screening or test result on smoking intensity. Regarding smoking cessation and continued abstinence, studies showed that study participation, which could be a proxy for participation in a lung screening program, may have influenced smoking cessation. Below, we describe evidence showing the (1) impact of LDCT vs. CXR or no screening on smoking cessation and intensity (using data from RCTs); (2) impact of abnormal (true positive and false positive) or indeterminate screening results vs. normal results on smoking cessation, abstinence, and relapse (using data from RCTs and uncontrolled studies); and (3) potential impact of study participation (regardless of arm assignment or treatment) on cessation, abstinence, and relapse.

One RCT (DLCST; described in two publications) and one report of participants from an RCT (NELSON) showed mixed results regarding smoking cessation when comparing participants who were screened with those who were not screened.[145, 147, 148] In a report of the 4,075 participants from the DLCST, the quit rate at year 1 among baseline current smokers was almost identical for the LDCT and no screening groups (11.9% vs. 11.8%, p=0.95).[145] The annual proportion of nonsmokers increased in each of the five study years but was not different across study arms (LDCT vs. no screening: baseline: 25% vs. 23%, p=0.213; year 2: 31% vs. 30%, p=0.537; year 3: 36% vs. 37%, p=0.599; year 4: 40% vs. 40%, p=0.827; year 5: 43% vs. 43%, p=0.909).[147] Conversely, in a paper reporting on 1,284 participants from the NELSON trial, both

study arms showed relatively high abstinence rates (compared with general adult population rates of 3% to 7%), but the control arm was somewhat higher (LDCT vs. no screening on smoking abstinence at 2 years–no smoking in past 7 days: 15.1% vs. 19.8%, p=0.04; fewer than five cigarettes within 2 weeks of quit date: 14.5% vs. 19.1%, p=0.04; fewer than five cigarettes since quit date: 13.9% vs. 18.7%, p=0.03).[148] This same analysis of NELSON trial participants showed no influence of LDCT screening on smoking intensity compared with no screening (reduced intensity: 53.1% vs. 53.8%, p=0.23; increased intensity: 17.7% vs. 13.8%, p=NR; remained stable: 29.2% vs. 32.4%, p=NR).[148]

One RCT (DLCST, N=3,745) and one paper reporting on screening arm participants from the NLST showed some evidence that screening results (positive or indeterminate vs. normal) may increase smoking cessation and decrease relapse.[145, 149] From the analysis of the 16,964 screening arm participants from the NLST, any false-positive result was associated with a greater point abstinence (first report of no longer smoking: HR, 1.23 [95% CI, 1.13 to 1.35]) and sustained abstinence (for at least 6 months: HR, 1.28 [95% CI, 1.15 to 1.43]) among smokers. In addition, recent quitters with at least one false-positive result were less likely to relapse than those with negative results (HR, 0.72 [95% CI, 0.54 to 0.96]).[149] Among the 3,745 DLCST participants with complete data on smoking habits, baseline smokers with positive results were more likely to quit than those with negative results (17.7% vs. 11.4%, p=0.04) and baseline ex-smokers were with positive results were less likely to relapse than those with negative results (4.7% vs. 10.6%, p<0.01).[145]

In four uncontrolled studies that compared positive or indeterminate vs. normal screening results, outcomes for smoking cessation and relapse were mixed.[150-153] A study of 2,078 ELCAP participants reported that those with negative results had higher cumulative point abstinence than those with any positive result (HR, 1.39 [95% CI, 1.01 to 1.90]; p<0.05) but did not have higher prolonged abstinence (HR, 1.34 [95% CI, 0.90 to 1.99]).[150] From the NELSON trial, a random sample of 990 male smokers with indeterminate results made more quit attempts than those with negative test results (1.9 +/- 2.7 attempts vs. 1.5 +/- 2.0 attempts, p=0.016), but there was no difference in point (12.2% vs. 10.4%, p=0.39) or prolonged (11.5% vs. 8.9%, p=0.19) abstinence.[153] Among 1,365 participants from the Mayo Lung Study, an abnormal result among baseline smokers was predictive of smoking abstinence (OR, 1.37 [95% CI, 1.12 to 1.67]; p=0.002) but not among baseline ex-smokers.[152] Among a cohort of 2,094 baseline active smokers from the PLuSS study, those who received a referral to further evaluation (e.g., additional scans) as a result of any non-normal initial LDCT result, compared with those with no referral, reported more smoking cessation. The most pronounced difference compared those with referral for results with moderate to high suspicion for cancer (delta, reported quit attempts 18.8% [95% CI, 11.1% to 26.5%]; reported quit more than 30 days, 17.7% [95% CI, 9.4% to 26.0%]; reported quit more than 30 days without relapse at 1 year 12.2% [95% CI, 4.9% to 19.5%]).[151]

Two uncontrolled studies[154, 155] reported the impact of screening (or study) participation on cessation, relapse, or motivation to quit. Among 1,473 baseline current smokers in the Mayo Lung Study, 14.9% reported abstinence at 1 year of followup, compared with 5 to 7 percent in the general population.[154] Finally, a description of reasons for study participation among 144 LSS participants and 169 NLST participants suggests that those willing to participate in a

screening program might be more open to receiving cessation counseling.[155] Both studies concluded that LDCT screening may be a "teachable moment" with regard to smoking cessation. One RCT (DLCST, N=4,075)[147] and one sample of RCT participants (NELSON, N=1,284)[148] also suggested that study participation, which could represent participation in a screening program, may, in and of itself, increase smoking cessation rates.

We did not find eligible studies reporting whether smoking behavior after LDCT differs for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors.

Psychosocial Harms

Four RCTs (DLCST, NELSON, NLST, and UK Lung Cancer Screening [UKLS] trial, 12,096 total participants), reported in six publications,[117, 156-160] one uncontrolled cohort study (PLuSS, 400 participants),[161] and two studies of participants from the screening arm of an RCT (NELSON, 630 participants;[162] UKLS, 1,589 participants[163]) included an evaluation of potential psychosocial consequences of undergoing LDCT screening for lung cancer. These studies evaluated general health-related quality of life (HRQoL; 3 studies),[156, 159, 162] anxiety (8 studies),[117, 156-162] depression (2 studies),[117, 157] distress (3 studies),[117, 159, 162] and other psychosocial consequences of LDCT screening (5 studies).[117, 158, 160, 161, 163] Taken together, there is moderate evidence to suggest that, compared with no screening, individuals who receive LDCT screening do not have worse general HRQoL, anxiety, or distress over two years of followup. Some evidence suggests differential consequences by screening result such that general HRQoL and anxiety were worse, at least in the short term, for individuals who received true-positive results compared with other screening results; distress was worse for participants who received an indeterminate screening result compared with other results. The strength of evidence is low for other psychosocial consequences, largely because of unknown consistency, imprecision, and only one or two studies assessed outcomes. The following paragraphs describe evidence for LDCT vs. no screening or CXR and for comparisons of people with different LDCT screening results (e.g., comparing those with false-positive results vs. negative results), on general HRQoL, anxiety and depression, distress, and other psychosocial consequences.

General Quality of Life

To measure general HRQoL, the NELSON trial used the SF-12 and EuroQol visual analog scale [EQ-5D VAS] questionnaires.[159] The SF-12 consists of a Physical Component Score [PCS] and a Mental Component Score [MCS]; scores range from 0 (lower level of health) to 100 (higher level of health). The EQ-5D VAS asks participants to rate their health on a scale of 0 (worst imaginable status) to 100 (best imaginable status). Regarding general HRQoL, the NELSON trial reported no statistically significant differences over 2 years of followup between individuals who had LDCT screening for lung cancer and those who were assigned to a no-screening control arm (mean PCS from the SF-12: 49.95 screening arm vs. 49.07 control arm; mean MCS from the SF-12: 52.50 screening arm vs. 51.69 control arm; mean EQ-5D VAS: 79.53 screening arm vs. 77.45 control arm; 931 participants).[159] The authors used a minimal important difference (MID) threshold of at least half of a standard deviation of the mean to determine whether the differences between assessment points were clinically relevant. Moreover, no differences in HRQoL were

observed for individuals with a negative or indeterminate result from baseline to 6 months after the second-round screening (mean PCS: 50.20 negative result vs. 49.24 indeterminate result; mean MCS: 52.70 negative result vs. 51.82 indeterminate result; mean EQ-5D VAS: 80.12 negative result vs. 78.22 indeterminate result). Similarly, findings from the NLST suggest no statistically significant differences in general HRQoL (measured using a PCS and MCS derived from the SF-36) from baseline to 6 months followup between individuals with false-positive, positive for significant incidental findings, or negative screen results.[156] Compared with those receiving negative results and after adjusting for potential confounders (e.g., baseline age, sex, race/ethnicity), regression estimates were not statistically significantly different for PCS or MCS from baseline to short-term (1 month) and long-term (6 months) followup for those receiving false-positive results (PCS baseline to 1 month: 0.46, 95% confidence limit [CL], -0.04 to 0.97; PCS baseline to 6 months: 0.30, 95% CL, -0.27 to 0.87; MCS baseline to 1 month: -0.22, 95% CL, -0.82 to 0.37; MCS baseline to 6 months: 0.03, 95% CL, -0.65 to 0.70) or significant incidental findings results (PCS baseline to 1 month: 0.13, 95% CL, -0.62 to 0.88; PCS baseline to 6 months: -0.16, 95% CL, -1.01 to 0.69; MCS baseline to 1 month: -0.04, 95% CL, -0.93 to 0.84; MCS baseline to 6 months: 0.29, 95% CL, -0.72 to 1.31). However, short-term and long-term HRQoL were worse for individuals receiving true-positive results compared with those receiving other screening results. Regression analyses revealed statistically significant changes for those receiving true-positive results compared with those receiving negative results from baseline to 1 month for MCS (-3.95, 95% CL, -5.87 to -2.04) and baseline to 6 months for PCS (-7.02, 95% CL, -8.80 to -5.24) and MCS (-4.15, 95% CL, -6.27 to -2.03) but not for baseline to 1 month for PCS (-1.18, 95% CL, -2.81 to 0.45). These findings should be interpreted with the awareness that participants in this trial received extensive counseling as part of the consent process, including information about the high risk of a false-positive screen and related followup. General HRQoL did not differ between those receiving LDCT screening and those receiving a CXR. Compared with participants randomized to receive a CXR, those who were randomized to LDCT screening did not exhibit better or worse general HRQoL (PCS baseline to 1 month: 0.07, 95% CL, -0.44 to 0.59; PCS baseline to 6 months: 0.50, 95% CL, -0.06 to 1.07; MCS baseline to 1 month: 0.23, 95% CL, -0.37 to 0.83; MCS baseline to 6 months: 0.07, 95% CL, -0.61 to 0.74).[156]

Anxiety and Depression

Some evidence suggests individuals experience short-term increases in anxiety after undergoing LDCT screening for lung cancer, but these increases tend to diminish over time. In an uncontrolled cohort study, the PLuSS,[161] participants who had an indeterminate screening result had increased state anxiety (i.e., anxiety about an event, measured using the State-Trait Anxiety Inventory [STAI]) at 1 to 2 weeks postscreen (mean [*M*]=37.7, standard deviation [*SD*]=13.8) and 6 months (*M*=37.3, *SD*=12.6) compared with baseline (*M*=34.4, *SD*=12.3), but state anxiety returned to baseline levels 12 months after screening (*M*=35.3, *SD*=13.5). For reference, a score of 39 to 40 or 54 to 55 for older adults, has been suggested for detecting clinically meaningful symptoms of state anxiety.[164] In multivariable analysis, the regression coefficient for the interaction between an indeterminate screening result and survey time (7.50; standard error [SE], 2.00) and the interaction between an indeterminate screening result and survey time squared (-1.41; SE, 0.39) were both statistically significant at $p < .001$. Analyses for trait anxiety (i.e., anxiety as a personal characteristic) did not yield any statistically significant associations for the

survey time or screening result (negative, indeterminate, or suspicious result) variables. Findings from the NLST suggest differential anxiety levels (measured using STAI Form Y-1) by screening result such that anxiety was substantially higher (worse) among individuals who received a true-positive result (1-month score: *M*=41.06, *SD*=15.10; 6-month score: *M*=37.69, *SD*=12.04) compared with those who received false-positive (1-month score: *M*=34.34, *SD*=12.58; 6-month score: *M*=33.92, *SD*=12.77), significant incidental findings (1-month score: *M*=33.83, *SD*=12.68; 6-month score: *M*=33.19, *SD*=12.41), or negative screen results (1-month score: *M*=32.67, *SD*=11.97; 6-month score: *M*=32.76, *SD*=12.36).[156] Anxiety did not differ by screening arm; compared with participants randomized to receive a CXR, those who were randomized to LDCT screening did not exhibit better or worse anxiety (STAI ratio at 1 month: 1.01, 95% CL, 0.93 to 1.10; STAI ratio at 6 months: 1.02, 95% CL, 0.93 to 1.12). Conversely, data from the DLCST did not indicate that undergoing LDCT screening for lung cancer increases the risk of receiving prescription medications for anxiety or depression during the period from baseline to 3 years followup compared with the control arm (adjusted HR: 1.00 [95% CI, 0.90 to 1.12]).[157] As the authors note, the use of prescriptions would likely identify only more severe anxiety and depression.

Distress

Research also suggests short-term increased distress levels following LDCT screening for lung cancer for individuals receiving an indeterminate result.[162] In the NELSON trial, the 15-item Impact of Events Scale (IES) was tailored to measure lung cancer–specific distress. In addition to producing a total summary score (range: 0-75), the IES yields scores for the intrusive subscale (e.g., having trouble staying asleep because pictures or thoughts about the event came to mind; range: 0-35) and avoidance subscale (e.g., trying to remove the event from memory; range: 0-40). In the short term (2 months after a baseline scan), the NELSON trial data revealed that distress levels were higher (worse) among individuals who received an indeterminate result (IES total score: *M*=8.3, *SD*=11.3) compared with those who received a negative result (IES total score: *M*=2.4, *SD*=5.5). These differences were both statistically significant ($p<.01$) and considered clinically relevant by the authors (using a MID threshold of at least half of a standard deviation of the mean),[162] although the effect was small because the average IES total score for those with indeterminate results was just 8.3 on a scale that ranges from 0 to 75. For those who received an indeterminate result, distress levels returned to near-baseline levels 2 years after baseline screening.[159] Similarly, findings from the UKLS Trial suggest higher levels of distress among individuals who undergo LDCT screening for lung cancer compared with no screening, but these effects were short term and were only among individuals with low scores at baseline (intervention arm: *M*=8.54 [95% CI, 8.44 to 8.64]; control arm: *M*=8.26 [95% CI, 8.16 to 8.36]).[117] Data from this trial also suggest differential distress levels by screening result; individuals who received a multidisciplinary team referral (indicating a major lung abnormality) reported the highest distress.

Other Psychosocial Consequences

Participants in the DLCST were assessed for other potential psychosocial consequences of LDCT screening, measured using the Consequences of Screening (COS) and Consequences of Screening in Lung Cancer (COS-LC).[158, 160] COS scales included anxiety (range of values: 0-18),

behavior (range: 0-21), dejection (range: 0-18), and sleep (range: 0-12); single items included busy to take mind off things (range: 0-3), less interest in sex (range: 0-3), and self-rated health (range: 0-4). COS-LC scales included self-blame (range: 0-15), focus on (airway) symptoms (range: 0-24), stigmatization (range: 0-12), introvert (range: 0-18), harm of smoking (range: 0-6), and anxiety (anxiety for COS-LC was the same scale used in COS plus an extra item: shocked; range: 0-21); single items included busy to take mind off things (range: 0-3), less interest in sex (range: 0-3), and self-rated health (range: 0-4). For reference, higher scores indicate more negative psychosocial consequences. Among participants with negative screening results in the LDCT screening arm and those in the control arm, mean scores significantly worsened from the prevalence round (prerandomization to study arm) to the incidence round (postrandomization) on the behavior scale (mean increase: 1.0535 screen arm, 1.1962 control arm), dejection scale (mean increase: 0.4076 screen arm, 0.5371 control arm), and sleep scale (mean increase: 1.0271 screen arm, 1.1025 control arm) and on two single items: busy to take mind off things (mean increase: 0.0539 screen arm, 0.0760 control arm) and less interest in sex (mean increase: 0.2253 screen arm, 0.1811 control arm; all $p < .01$).[160] The significantly worse scores for the three scales persisted for another three rounds of screening. At the incidence round, scores were worse for the control arm than for the LDCT screening arm for three COS scales: anxiety (*M*=1.50, *SD*=2.52 screen arm vs. *M*=1.71, *SD*=2.79 control arm), behavior (*M*=1.76, *SD*=2.85 screen arm vs. *M*=2.02, *SD*=3.04 control arm), and dejection (*M*=1.61, *SD*=2.71 screen arm vs. *M*=1.88, *SD*=2.98 control arm). Scores were also worse for the control arm for four COS-LC scales: self-blame (*M*=2.32, *SD*=3.53 screen arm vs. *M*=2.62, *SD*=3.75 control arm), focus on (airway) symptoms (*M*=3.30, *SD*=3.58 screen arm vs. *M*=3.80, *SD*=3.93 control arm), introvert (*M*=1.89, *SD*=1.76 screen arm vs. *M*=2.22, *SD*=2.96 control arm), and anxiety (*M*=1.55, *SD*=2.67 screen arm vs. *M*=1.77, *SD*=2.93 control arm). The authors note that one possible explanation for the worse psychosocial consequences in the control arm is that compared with participants in the LDCT screening arm control arm participants did not benefit from the reassurance that a normal screening result may offer. Although these differences meet the threshold for statistical significance, it is unclear whether they are clinically meaningful. Using at least a half of a standard deviation of the mean as a threshold for determining the MID,[165] we found that none of the statistically significant differences would be considered clinically meaningful.

The UKLS Trial assessed participants' satisfaction with their decision to participate in an LDCT trial using the Satisfaction with Decision Scale.[117] This six-item scale has five response categories that span from strongly disagree to strongly agree; items are summed and averaged for a total possible score ranging from 1 to 5. The authors dichotomized this score such that a score less than 5 is considered "not very satisfied" and a score of 5 is considered "very satisfied." Findings suggest decision satisfaction varied by LDCT screening result. In the short term (2 weeks after receiving scan results), 57 percent of participants who were positive for multidisciplinary team referral were very satisfied with their decision to participate in the trial, whereas 46 percent with a negative result, 44 percent with a negative result who also had an incidental finding, and 36 percent with a positive for repeat scan result were very satisfied with their decision. In the long term (10 to 27 months after recruitment), 71 percent of participants with a true-positive result were very satisfied with their decision to participate in the trial compared with 39 percent with a true-negative result, 45 percent with an incidental finding, and 41 percent with a false-positive result.

The UKLS Trial also assessed perceived concern about the LDCT scan result, which was used to represent perceived threat.[163] The authors examined whether there was an association between perceived concern and expectation-result congruence. Two weeks after they received their LDCT scan result, participants completed a questionnaire that included a single-item measure of perceived concern: "How concerned were you by your CT scan result?" Participants responded by selecting "not at all concerned," "not very concerned," "fairly concerned," or "very concerned." At baseline, participants were asked to report their expected scan result: "normal/clear scan result" (renamed "negative") or "unclear or abnormal scan result." Actual scan results were categorized as negative or positive for a repeat scan or MDT referral. Four expectation-result congruence groups were formed: (1) expected negative, (2) unexpected followup, (3) unexpected negative, and (4) expected followup. Findings indicate that although most (82%) of the 1,589 participants expected a negative result, 48 percent actually had a negative result. There was a statistically significant association between perceived concern about the LDCT scan result and expectation-result congruence ($p<.001$). Participants who received an expected negative result were statistically significantly less concerned (57% not at all concerned) about their scan result compared with those who did not have an expected negative result ($p<.001$). Participants who received an unexpected followup result reported more concern (54% fairly or very concerned) compared with those with an expected negative result (22% fairly or very concerned) and those with an unexpected negative result (36% fairly or very concerned)($p<.001$). Among those who expected a followup result, 65 percent reported they were fairly or very concerned. Younger age, those in the most deprived group (vs. the most affluent, measured using the Index of Multiple Deprivation), and those with an experience of lung cancer were more concerned about the result (all $p=.01$).

The PLuSS assessed fear of lung cancer and perceived risk of lung cancer among participants who had LDCT screening.[161] Three questions, adapted from the Psychological Consequences Questionnaire, were used to assess the effects of screening on fear. The five-point response scale ranged from "never" to "most of the time." Scores were summed to obtain a total score; higher scores suggested greater fear of cancer. Average fear of lung cancer scores varied by LDCT screening result. Fear of lung cancer scores remained fairly level over time for participants with negative screen results (*M*=7.0, *SD*=2.5 initial; *M*=7.0, *SD*=2.4 at postscreen; *M*=6.5, *SD*=2.4 at 6-month followup; *M*=6.7, *SD*=2.3 at 12-month followup) or indeterminate screen results (*M*=7.2, *SD*=2.8 initial; *M*=7.5, *SD*=2.7 at postscreen; *M*=7.1, *SD*=2.6 at 6-month followup; *M*=7.1, *SD*=2.7 at 12-month followup). Among participants with a suspicious screen result, fear of cancer increased after screening. This increase diminished over time but did not return to baseline levels by the 12-month followup survey (*M*=6.4, *SD*=2.3 initial; *M*=8.5, *SD*=2.6 at postscreen; *M*=7.4, *SD*=3.0 at 6-month followup; *M*=7.1, *SD*=2.5 at 12-month followup). The authors also highlighted that fear of lung cancer did not diminish over time for participants with a negative screen result, as might be expected, and that perhaps a negative result does not bring peace of mind. Perceived risk of lung cancer was measured by asking participants how likely they believed it was that they had or will get lung cancer. Participants indicated their risk on a scale from no chance (0%) to certain (100%). As for perceived risk of lung cancer, average scores also varied by LDCT screening result. Perceived risk of lung cancer decreased after screening for those with a negative screen result (*M*=17.1, *SD*=20.4 initial; *M*=11.2, *SD*=20.2 at postscreen; *M*=13.1, *SD*=20.8 at 6-month followup; *M*=13.1, *SD*=19.9 at 12-month followup). For those with an indeterminate result, perceived risk increased at postscreen (*M*=20.1, *SD*=25.0

compared with *M*=18.9, *SD*=22.9 initial), decreased at 6 months (*M*=14.8, *SD*=19.7), and increased to baseline levels at 12-month followup (*M*=18.9, *SD*=25.2). For those with a suspicious screening result, perceived risk nearly doubled at postscreen (*M*=34.5, *SD*=28.0 compared with *M*=18.6, *SD*=15.7 initial), then decreased at 6 months (*M*=30.3, *SD*=28.0), and increased at 12-month followup (*M*=31.2, *SD*=28.9).

Subgroups

We did not identify studies reporting whether psychosocial consequences of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors.

Incidental Findings Leading to Additional Tests and Subsequent Harms

Summary

Studies reported a wide range of screening-related incidental findings (4.4% to 40.7%) that were deemed significant and/or requiring further evaluation (**Appendix E Table 3**). Rates varied considerably in part because there was no consistent definition of what constitutes an incidental finding nor which findings were "actionable" or "clinically significant." Older age was associated with a greater likelihood of incidental findings. Common incidental findings included coronary artery calcification, aortic aneurysms, emphysema, and infectious and inflammatory processes. Other common findings were masses, nodules, or cysts of the kidney, breast, adrenal, liver, thyroid, pancreas, spine, and lymph nodes. Cancers involving the kidney, thyroid, or liver were ultimately diagnosed in 0.39 percent of NLST participants in the LDCT arm during the screening period. Incidental findings led to downstream evaluation including consultations, additional imaging, and invasive procedures with associated costs and burdens. The benefits of incidental detection of nonlung cancer conditions are uncertain.

Detailed Results

Evidence From Uncontrolled Studies

Most of the current evidence regarding incidental findings comes from uncontrolled studies because incidental findings are not easily defined for an unscreened (control) population. We found six fair-quality uncontrolled studies (n=27,237 total participants) that described rates of "significant" incidental findings in LDCT-screened populations.[38, 117, 137, 166-168] Two of these used data from trials (NLST and UKLS).[117, 166] The other four were U.S.-based cohort studies. Some of these studies reported additional data regarding followup evaluations and findings.

A study of NLST participants assigned to the LDCT screening arm (three rounds) who were enrolled at American College of Radiology Imaging Network centers (n=17,309) found that 58.7 percent of participants had one or more extrapulmonary findings, including 19.6 percent with findings categorized by radiologists as "potentially significant."[166] The frequency of these "potentially significant" abnormalities was highest for cardiovascular findings (e.g.,

atherosclerotic calcifications and aortic aneurysms) (8.5%), followed by renal (2.4%), hepatobiliary (2.1%), adrenal (1.2%), and thyroid (0.6%). These findings led to additional specialty consultations, imaging, invasive testing, and surgery. Extra-thoracic cancers, including kidney, thyroid, and liver cancers, were diagnosed in 67 (0.39%) participants during the screening period. By organ type, the ratio of malignancy to incidental LDCT lesion was highest for the thyroid (1 cancer per 14 findings) followed by kidneys (1 cancer per 37 findings).

In the United Kingdom Lung Cancer Screening Trial, among 1,994 participants screened with a single round of LDCT, the rate of significant incidental findings not related to thoracic malignancy that were referred back to the participant's general practitioner was 6.4 percent.[117]

The Veterans Health Administration Lung Cancer Screening Demonstration Project reported incidental findings at eight demonstration sites after a single round of screening. They found that 40.7 percent of participants (n=2,452) had one or more incidental findings deemed likely to require followup or further evaluation.[38] The most common findings included coronary artery calcification, emphysema, abdominal abnormalities and masses (14%), aortic dilation (8.3%), inflammatory or interstitial processes (25.4%), and thyroid nodules (2.4%). The rate of incidental findings deemed likely to need followup varied widely across the eight demonstration sites from 20.0 to 63.4 percent.

A study of 320 patients undergoing one round of LDCT screening at a tertiary U.S. lung cancer screening program reported the frequency and types of incidental findings along with additional data on subsequent evaluation that was driven by prespecified care paths.[167] If using a broad definition of incidental findings, the vast majority (94%) of the 320 patients had some type of incidental abnormality noted by radiologists in the LDCT report. These types of incidental abnormalities included calcification of coronary arteries (56%) or the aorta (21%), emphysema (50.6%), aortic dilation (8.1%), adrenal nodules (3.8%), renal cysts (2.5%), and thyroid nodules (4.7%). Using a narrower definition, we see that 15 percent of participants had incidental findings categorized as "concerning" and underwent further evaluation that included a variety of nonpulmonary subspecialty consultations, lab tests, imaging studies, and invasive procedures. Five fine-needle aspirations of thyroid nodules were performed. One patient had a total thyroidectomy that revealed a (benign) hyperplastic nodule and multinodular goiter. Evaluation of two suspicious renal masses led to diagnosis of two renal cell carcinomas (grade 3).

Another U.S. cohort study found that 14 percent of 1,520 patients assigned to three rounds of annual screening had incidental nonpulmonary findings of significance that required further evaluation.[168] The most common nonpulmonary findings (with frequency >1%) were abdominal aortic aneurysm (3.4%), adrenal masses (2.3%), indeterminate renal masses (2.2%), renal calculi (1.6%), and breast nodules (1.1%). Several nonlung cancers were eventually diagnosed including two carcinoid tumors, four renal cell cancers, three breast cancers, two lymphomas, two gastric tumors, and one pheochromocytoma.

PLuSS enrolled 3,642 participants assigned to two rounds of annual LDCT screening and followup. A total of 4.4 percent had "significant" incidental findings, which were not otherwise characterized.[137]

Evidence From RCTs

We identified one eligible controlled trial.[169] Because of concerns that LDCT could lead to overdiagnosis of thyroid cancer through increased incidental detection, the study used data from the NLST (n=53,248) to examine the association of LDCT screening and thyroid cancer risk.[169] It reported a total of 60 thyroid cancers (37 in the LDCT group vs. 23 in the CXR group), finding a significant increase in thyroid cancer incidence in the LDCT arm compared with the CXR arm during the 3 years of active screening (HR, 2.19 [95% CI, 1.07 to 4.47]) but not during subsequent years of nonimaging observation (HR, 1.08 [95% CI, 0.49 to 2.37]).

Subgroup differences. We identified one study that examined age differences in incidental findings. In this study of 26,722 participants in the LDCT screening arm of the NLST, negative screening results with "clinically significant abnormalities" were more common in the screened cohort over age 65 years compared with those under age 65 (9.2% vs. 6.9%, p< 0.0001).[64]

Key Question 6a. How Effective is Surgical Resection or SBRT for the Treatment of Early (Stage I) NSCLC?
Key Question 6b. Does Effectiveness Differ for Subgroups Defined by Age, Sex, Race/Ethnicity, or Presence of Comorbid Conditions?

Summary

No RCTs comparing surgical resection or SBRT with no treatment for stage I NSCLC were identified. Twenty-seven uncontrolled studies evaluating surgical resection (n=147,837 patients with stage I NSCLC),[170-196] including 6 from the prior review,[190-195] (**Appendix E Tables 4** and **5**) and 13 uncontrolled studies evaluating SBRT (n=8,697 patients with stage I NSCLC)[185, 196-207] (**Appendix E Tables 4** and **6**) for the treatment of stage I NSCLC were included for KQ 6 for presentation to the USPSTF; additional studies were subsequently identified in update searches and literature surveillance and are described below in the *Update Search Summary* sections. Results of those studies were similar to what was identified by the original search yield. The studies from the original search yield were uncontrolled analyses of prospectively collected data from registries or databases (e.g., National Cancer Database) or primary studies conducted at one or more institutions. Five surgical resection studies[177, 179, 181, 185, 194] and one SBRT study[185] were rated as good quality; the remaining studies were rated fair quality (**Appendix D Table 1**). Seven surgery studies[172, 181, 184, 186, 187, 191, 192] and 1 SBRT[204] study reported survival outcomes among subgroups.

The strength of evidence for the effectiveness of surgical resection and SBRT for the treatment of stage I NSCLC is moderate and low for benefit, respectively, downgrading primarily because the evidence came from uncontrolled cohort studies and for imprecision. Clinical characteristics of the NSCLC diagnoses and operability of tumors, surgical approaches, and SBRT treatment characteristics among studies and over time resulted in imprecise results, despite an overall substantial sample size for the question related to surgical resection.

Surgical Resection

Description of Included Studies

Twenty-seven studies evaluated the effectiveness of surgical resection for the treatment of stage I NSCLC. Sample sizes ranged from 540[177] to 54,350.[178] Of the 27 studies, 14 were primary studies conducted between 1983 and 2012 in the United States,[170, 172, 174, 176, 181, 182] Japan,[173, 179, 184, 191, 193, 195] the United Kingdom,[177, 181] and Italy[171] (n=16,671 stage I NSCLC patients). The remaining 13 studies were analyses of 131,166 stage I NSCLC patients in the Surveillance, Epidemiology, and End Results (SEER) database between 1988 and 2012 (k=5 studies);[175, 180, 183, 188, 192] the National Cancer Database (NCDB) between 2003 and 2012 (k=5 studies);[178, 185-187, 189] the Veteran's Affairs Informatic and Computing Infrastructure (VINCI) database between 2006 and 2015; and cancer registries in Norway (1993 to 2002),[194] and Japan (2004).[190] The SEER program and database, initiated in 1973 by the National Cancer Institute, includes data from a network of cancer registries that represent approximately one-third of the U.S. population,[208] and the NCDB is a nationwide oncology outcomes database for more than 1,500 Commission on Cancer–accredited cancer programs in the United States and Puerto Rico. The NCDB is a joint effort by the American College of Surgeons and the American Cancer Society, captures approximately 70 percent of all newly diagnosed cases of cancer in the United States, and includes over 34 million records.[209] Six of the studies[190-195] were included in the prior review.[47]

Most studies included patients with mean or median ages between 63 and 69. Exceptions included two studies of SEER data focused on patients with stage IA NSCLC who were 75 years or older[180] or who received sublobar resection (SLR),[188] and a study of patients from the United Kingdom who received wedge resection;[177] limited resections, rather than lobectomy, are often indicated for elderly patients with comorbidities or poor pulmonary reserve. The percentage of male patients in most studies ranged from 36 percent[186] to 72 percent.[171] Ninety-six percent of the patients in the analysis of VINCI data (i.e., veterans) were male.[196] Four studies had mean or median followup times of less than 3 years,[177, 185, 188, 210] five had more than 5 years of followup on average,[174, 176, 181, 187, 193] and 11 did not report mean or median length of followup.[170, 175, 178, 180, 182, 186, 189, 191, 192, 194, 195] The other 7 studies had median followup between three and five years.

Patients were enrolled based on both clinical (k=12 studies) and pathologic (k=11 studies) stage. Study populations were restricted to patients with stage I NSCLC, or they presented results for subgroups of patients defined by stage. One study did not specify type of staging,[192] two studies did not specify staging at enrollment but provided results for both clinical and pathologic staging,[190, 195] and one study categorized patients by pathologic stage when available (clinical stage, otherwise).[178] Eight of the 27 studies included only patients with stage IA NSCLC.[179, 180, 183, 184, 187-189, 192] Most studies included multiple histologic subtypes of stage I NSCLC. Four studies included only patients with adenocarcinoma, the most common subtype; three of the four studies were further restricted to stage IA adenocarcinoma NSCLC,[179, 183, 184] and the fourth was restricted to adenocarcinoma NSCLCs with lepidic features (i.e., well-differentiated, noninvasive tumor growth).[186] Three studies included only patients who received a lobectomy,[173, 175, 185] one included only patients who received SLR,[188] and one included only patients who received wedge resection.[177] All other studies included multiple surgical approaches. In one study, patients were

categorized by whether they received video-assisted thoracoscopic (VATS) or open lobectomy.[182]

Detailed Results

Long-term survival rates varied across study populations, overall and among subgroups defined by various surgical approaches and tumor characteristics in 27 studies. One fair quality study was conducted among a highly selected population of patients 75 years of age or older with stage IA NSCLC[180] and a good quality study only presented results for patients with pathologic stage I NSCLC by cardiac risk score category[181]; both are described in the subgroups section below. Of the remaining 25 studies, 14 report results for stage I NSCLC (n=139,562),[170-172, 174-178, 182, 185, 186, 191, 194, 196] 12 report results for stage IA NSCLC (n=49,741),[173, 179, 183, 184, 187-190, 192-195] and 4 report results for pathologic stage IB NSCLC (n=4,852).[173, 190, 194, 195]

Across all surgical approaches in 14 studies of stage I NSCLC, the 5-year overall survival (OS) ranged from 51 percent in a good quality Norwegian database study of 1,375 patients from 1993 to 2002[194] to 86 percent in a fair quality Japanese study of 713 patients from 1994 to 2003;[191] both studies evaluated surgical resection as the intervention (rather than specific surgical approaches). Among 54,350 patients in the NCDB from 2003 to 2006, the 5-year OS for surgical resection was 61 percent for pathologic and 57 percent for clinical stage I NSCLC.[178] In a fair quality analysis of SEER data from 2004 to 2010, the 5-year OS ranged from 53 percent to 75 percent among 16,315 stage I NSCLC patients who received lobectomy, depending on tumor size and visceral pleural invasion (VPI) status;[175] three other studies reported 5-year OS for lobectomy of 59 percent in 1,781 healthy patients matched to healthy patients who received SBRT[185] and 70 percent in both the NCDB (2003-2006; n=1,991)[186] and VA (2006-2015; n=3,620)[196] databases. Except for one analysis of SEER data from 1988 to 1997, where the 5-year OS was 58 percent among 10,761 patients, all other studies that evaluated surgical resection for stage IA NSCLC were conducted in Japan[179, 184, 190, 195] or Norway[194] where the 5-year OS rates ranged from 65 percent[194] to 86 percent.[190] The 5-year OS rates for lobectomy among 11,990 patients in the NCDB (2003-2006) and 7,989 patients in SEER (2004-2012) with stage IA NSCLC were 66 percent[187] and 71 percent,[183] respectively. All of the studies that evaluated surgical resection for pathologic stage IB NSCLC were conducted in Japan[173, 190, 195] and Norway;[194] the 5-year OS rates ranged from 42 percent among 816 Norwegian patients (1993-2002)[194] to 69 percent among 2,398 Japanese patients in 2004.[190]

Ten studies reported survival rates for different types of or approaches to surgical resection. In one US study of lobectomy for clinical stage I NSCLC (n=963) in 2002-2011, the 5-year OS rate was significantly higher among patients who received VATS (78%) than patients who received open lobectomy (68%), but the difference decreased in a propensity score–matched analysis of the data.[182] In five studies, 5-year OS rates were statistically similar between surgical approaches, although rates were generally numerically higher for lobectomy compared with SLR approaches.[176, 179, 183, 186, 193] In one of the studies (n=614), there was also no difference between lobectomy and segmentectomy with respect to 5-year recurrence-free survival rates (71% [95% CI, 64% to 78%] and 70% [95% CI, 63% to 78%], respectively).[176] The 5-year lung cancer-specific survival (LCSS) was 84 and 81 percent for lobectomy and segmentectomy, respectively, in a SEER study of 7,989 pathologic stage IA patients in 2004-2012.[183] Lobectomy outperformed

SLR in two studies; the 5-year OS rates were 66 percent[187] and 70[196] percent for lobectomy and 51 percent[187] and 56[196] percent for SLR. In one of those studies (n=3,620 VA patients), the 5-year incidence of cancer death was 23 percent for patients who received lobectomy and 32 percent for patients who received SLR.[196] Lobectomy resulted in significantly higher 5-year OS rates than specific types of SLR in two additional studies. In one study among patients 75 years and older, the 5-year OS was 50 percent for lobectomy compared with 44 percent and 39 percent for segmentectomy and wedge resection, respectively; the 5-year cancer-specific survival (CSS) was also different by surgical approach (65%, 59%, and 53%, respectively).[180] In the other study of 7,034 patients in the NCDB (2003-2011), the 5-year OS rates were 70 percent, 60 percent, and 55 percent for lobectomy, segmentectomy, and wedge resection, respectively.[189]

The 5-year OS rates were higher among stage IA than stage IB NSCLC patients in four studies,[173, 190, 194, 195] regardless of whether the tumor staging was clinical or pathologic, and ranged from 64 percent[194] to 86 percent[190] for stage IA and 42 percent[194] to 69 percent[190] for stage IB. Three studies reported 5-year survival rates by tumor size, but each study used different categories (<2 vs. 2-3 vs. 3-5 cm;[175] ≤1 vs. 1-2 cm;[189] and ≤3 vs. 3-5 vs. >5 cm[194]), making it difficult to compare them directly. However, survival rates decreased as tumor size increased in all three studies. In one of the studies (which used SEER data from 16,315 patients from 2004 to 2010), investigators further stratified by VPI status.[175] Both the 5-year OS and LCSS rates were higher among patients without VPI than patients with VPI. Among patients with tumors <2 cm, the 5-year OS and LCSS rates were 75 percent and 88 percent, respectively, for patients without VPI; the rates were lower (70 percent and 84 percent, respectively) for patients with VPI. Similarly, among patients with tumors 3-5 cm, the 5-year OS and LCSS rates were 60 percent and 72 percent, respectively, for patients without VPI; the rates were lower (53% and 66%, respectively) for patients with VPI.[175] Finally, in a multisite study of 618 patients in Japan, 5-year OS was higher among patients who met node negative criteria post-surgery (96%) than patients who did not (83%), as was 5-year recurrence-free survival (97% and 76%, respectively).[179]

Subgroups

Seven studies evaluated the effectiveness of surgical resection among subgroups of patients with stage I NSCLC; one additional study included a highly selected population based on age 75 years or older.[180] Overall survival was higher among females,[184, 186, 187, 191, 192] younger patients,[184, 186, 187, 191, 192] white patients,[186] patients without comorbidities,[172, 181, 186, 187] and non- or light smokers[184, 191] than among males, older patients, black patients, patients with comorbidities, and smokers or heavy smokers, respectively.

Five-year OS rates were higher among females than males in three studies (91% vs. 83%,[191] 85% vs.74%,[184] and 63% vs. 53%,[192] respectively); 10-year overall survival was also higher among females (85%) than males (77%) in one Japanese study between 1994 and 2003.[191] In the NCDB from 2003 to 2006, the multivariable-adjusted HRs for females compared with males were 0.78 (95% CI, 0.67 to 0.90) among 1,991 patients with lepidic adenocarcinoma[186] and 0.76 (95% CI, 0.72 to 0.80) among 11,990 patients with clinical stage IA.[187] Five- and 10-year OS rates were higher among younger patients (i.e., <67 years of age) than older patients in both Japan[184, 191] and the United States and Europe.[181, 192] In a study restricted to 1,640 patients 75 years or older with

stage IA NSCLC, the 5-year OS was 50 percent for lobectomy, 44 percent for segmentectomy, and 39 percent for wedge resection.[180] In the NCDB from 2003 to 2006, there was a 46 percent increased risk of death for every 10 years of age (adjusted HR, 1.46; 95% CI, 1.35 to 1.59).[186] In the NDCB study of 1,991 patients with lepidic adenocarcinoma (2003-2006), black patients had a 45 percent increased risk of death compared with white patients (adjusted HR, 1.45; 95% CI, 1.07 to 1.96); risk of death was nonsignificantly lower among other nonwhite patients (adjusted HR, 0.90; 95% CI, 0.60 to 1.35) than white patients.[186]

The Charleson-Deyo Comorbidity Index is a validated method of predicting mortality by weighting comorbid conditions.[211] In an analysis of 11,990 clinical stage IA patients in the NCDB diagnosed between 2003 and 2006, the multivariable-adjusted HRs for patients with Charleson-Deyo Comorbidity Index scores of 1 and ≥2 were 1.21 (95% CI, 1.14 to 1.29) and 1.56 (95% CI, 1.44 to 1.68), respectively, when compared with patients with a score of 0.[187] Adjusted HRs were similar in the 2003-2006 analysis of patients with lepidic adenocarcinoma who had Charleson-Deyo Comorbidity Index scores of 1 and 2 (compared with 0).[186] Five-year OS among patients with and without COPD was similar (73% and 74%, respectively) in a U.S. study of 724 patients conducted from 1992 to 2010.[172] As another proxy for comorbidity, the Thoracic Revised Cardiac Risk Index (ThRCRI) is a prognostic tool that aims to identify patients at increased risk of major cardiac events after surgical resection for lung cancer.[181, 212, 213] A study of 1,370 patients with pathologic stage I NSCLC who underwent surgical resection in three U.S. and European thoracic surgery units from 2000 to 2011 were evaluated according to their ThRCRI class (A: score 0 to 1; B: score 1.5 to 2.5; and C: score > 2.5).[181] Five-year OS and CSS rates decreased as ThRCRI scores increased (class A: 66% and 77%, respectively; class B: 53% and 75%, respectively; class C: 35% and 55%, respectively). Likewise, median survival decreased with ThRCRI scores (98, 68, and 60 months for classes A, B, and C, respectively).[181]

Finally, 5- and 10-year OS rates were higher among nonsmokers (5-year OS: 91%; 10-year OS: 86%)[191] and patients reporting 0 to 20 pack-years of smoking (5-year OS: 86%)[184] than among smokers (5-year OS: 83%; 10-year OS: 76%)[191] and patients reporting more than 20 pack-years of smoking (5-year OS: 71%)[184] in two Japanese studies, one of which was restricted to patients with stage 1 adenocarcinoma NSCLC.[184]

Update Search Summary: Surgery Results

Nine fair-quality studies[214-222] identified through the update search evaluated the effectiveness of surgical resection for the treatment of stage I NSCLC (**Appendix E Tables 7** and **8**). Four studies analyzed 40,288 patients from the SEER database between 2000 and 2014, ensuring at least some overlap of patients among analyses;[214, 215, 219, 221] one study analyzed 14,545 patients from the California Cancer Registry between 2007 and 2013;[216] and one study analyzed 6,905 patients from the Polish National Lung Cancer Registry between 2007 and 2013.[217] Long-term survival rates varied substantially across study populations (5-year OS: 33% to 84.6%) but were similar to what was reported by the original search yield (5-year OS: 51% to 86%). Limited evidence based on a single study[222] also supported findings from the original search yield that sicker patients (i.e., those with clinically relevant comorbidities) generally did not fare as well in terms of survival as patients without comorbidities.

SBRT

Description of Included Studies

Thirteen studies evaluated the effectiveness of SBRT, also known as stereotactic ablative radiotherapy (SABR), for the treatment of stage I NSCLC (**Appendix E Tables 4** and **6**);[185, 196-207] all studies, except one good quality study,[185] were rated as fair quality. Sample sizes ranged from 39 to 4,454. Of the 13 studies, four studies analyzed data from the NCDB for patients diagnosed and treated with SBRT from 2003 through 2014.[185, 196, 199, 200, 202] In the largest NCDB analysis, 4,454 patients were treated with SBRT. The median followup time was 50 months (95% CI, 49 to 52 months) in the entire cohort, which also included 335 radiofrequency ablation patients; 46 percent of the cohort was male and the mean age was 74 years.[202] The three other NCDB analyses were among 1,781 otherwise healthy patients with operable tumors (i.e., surgery was not contraindicated because of patient risk factors),[185] 498 patients with inoperable tumors,[200] and 127 patients who were nonagenarians (i.e., ≥90 years old) at diagnosis.[199] The mean age of the healthy patients was 76 years, and the proportion of males ranged from 43 to 46 percent in the three analyses. One additional database study included 449 patients diagnosed between 2006 and 2015 from VINCI. A majority of patients were age 60 to 79 years at diagnosis, a majority were diagnosed between 2011 and 2015, and 97 percent were male.[196] In addition to the database studies, eight primary studies were conducted between 2003 and 2014 in the United States,[197, 204] Denmark,[203] Japan,[198, 201, 205] The Netherlands,[206] and Scandinavia.[207] Sample sizes ranged from 39[206] to 772,[204] and the reported percentage of male patients ranged from 45 in Denmark[203] to 72 in Japan.[198] The mean age of patients ranged from age 72 to 79 years; one study grouped patients by age at diagnosis (<75 years, ≥75 years) where the mean ages were age 67 and 81 years, respectively and is further described in the subgroups section below.[204] One study each included patients with only operable[201] or only inoperable[207] tumors; the operability of tumors was mixed (range of percent inoperable: 62% to 85%) or not described[198, 204] in the remaining studies.

Detailed Results

The 5-year OS was 33 percent among more than 4,000 patients in the NCDB[202] but was lower among patients with inoperable tumors (n=498) (30%)[200] or who were 90 years of age or older at diagnosis (n=127) (20%).[199] In a propensity score–matched analysis of otherwise healthy patients with operable tumors receiving lobectomy or SBRT in the NCDB that was rated as good quality, the 5-year OS was 29 percent among 1,781 patients receiving SBRT. In the same study, 235 SBRT patients who refused surgery were propensity score matched to lobectomy patients, and the 5-year OS was 40 percent.[185] Among 449 veterans in the VINCI database who received SBRT, the 5-year OS was 44 percent and the 5-year unadjusted cumulative incidence of cancer death was 45 percent.[196]

The median followup time among eight primary studies evaluating SBRT for stage I NSCLC ranged from 3 years (reported as 38 months[206]) in a Dutch study of 39 patients to 7 years in a U.S. study of 65 patients.[197] Among 57 patients in Scandinavia and 100 patients in Japan with inoperable tumors, the 5-year OS ranged from 30 percent (95% CI, 18% to 42%)[207] to 42 percent (95% CI, 33% to 52%),[205] respectively. Among Japanese patients with operable tumors, the 5-

year OS ranged from 54 percent (95% CI, 41% to 65%) among 65 patients[205] to 67 percent (95% CI, 50% to 79%) among 40 patients.[201] From studies with mixed or unknown patient populations in terms of operability, the 5-yr OS ranged from 35 percent among 136 patients in Denmark[203] to 66 percent among 65 patients in the United States.[197] In the U.S. study with median followup of 7 years and a mixed patient population, the 7-year OS was 47.5 percent and the 5- and 7-year progression-free survival rates were 49.5 percent and 38.2 percent, respectively.[197] The 5-year progression-free survival was similar in a Scandinavian study (52% [95% CI, 33% to 70%]).[207]

Subgroups

One study of 772 patients treated with SABR between 2004 and 2014 at The University of Texas MD Anderson Cancer Center compared survival between patients less than 75 years of age with patients 75 years or older.[204] The median overall survival was significantly higher among younger patients (61.2 months [95% CI, 53.2 to 69.2 months]) than among older patients (47.7 months [95% CI, 39.6 to 55.9 months]). Five-year OS rates decreased with increasing age in two separate analyses; among patients with mean ages in the 70s, 80s,[204] and 90s,[199] the 5-year OS rates were 52, 40, and 20 percent, respectively.

Update Search Summary: SBRT Results

Fourteen studies (13 fair-quality studies[223-235] and 1 good-quality study[236]) identified through the update search evaluated the effectiveness of SBRT for the treatment of Stage I NSCLC (**Appendix E Tables 7** and **9**). Two studies analyzed 27,795 patients from the NCDB between 2004 and 2014;[228, 232] and one study analyzed 378 patients from the Netherlands Cancer Registry.[231] Long-term survival rates varied substantially across study populations (5-year OS: 26% to 80%) but were similar to what was reported by the original search yield (5-year OS: 20% to 67%). Although survival varied by subgroups defined by clinical and patient characteristics, differences between subgroups based on sex, age, or NSCLC T-stage were not statistically significant.

Key Question 7a. What Are the Harms Associated With Surgical Resection or SBRT for the Treatment of Early (Stage I) NSCLC? Key Question 7b. Do the Harms Differ for Subgroups Defined by Age, Sex, Race/Ethnicity, or Presence of Comorbid Conditions?

Summary

No RCTs comparing surgical resection or SBRT with no treatment for stage I NSCLC were identified. Twenty-five uncontrolled studies evaluating surgical resection (n=737,775 patients with stage I NSCLC)[170, 173, 176, 177, 179, 182, 185, 189, 196, 237-252] for the treatment of stage I NSCLC were included for KQ 7 (**Appendix E Tables 4** and **5**) for presentation to the USPSTF; additional studies were subsequently identified in update searches and literature surveillance and are described below in the *Update Search Summary* sections. Results of those studies were similar to what was identified by the original search yield. Nine of the studies from the original search yield were previously included for KQ 6,[170, 173, 177, 179, 182, 185, 189, 196, 253] three were rated

good quality,[177, 179, 185] and 22 were rated fair quality (**Appendix D Table 1**).[170, 173, 176, 182, 189, 196, 237-252] Nine of the studies were uncontrolled analyses of prospectively collected data from the NCDB from 1998 to 2010, ensuring at least some overlap of patients among analyses.[189, 239, 240, 243-245, 250-252] Likewise, there were three analyses of SEER data from 1992 to 2009 that likely included some overlap of patients.[237, 241, 247] The remaining studies were from other registries or databases (e.g., VINCI) or primary studies conducted at one or more institutions. Five surgery studies reported harms outcomes among subgroups of patients defined by age, sex, and comorbidities.[189, 239, 242, 248, 251]

An additional 31 studies (32 articles) evaluating SBRT (n=17,353 patients with stage I NSCLC)[196-198, 202-207, 237, 241, 246, 251, 254-272] were also included for KQ 7 (**Appendix E Tables 4** and **6**) for presentation to the USPSTF; additional studies were subsequently identified in update searches and literature surveillance and are described below in the *Update Search Summary* sections; results of those studies were similar to what was identified by the original search yield. One of the studies was an RCT comparing two dosing regimens of SBRT (34 Gy in 1 fraction vs. 48 Gy in four consecutive daily fractions);[263] the remaining studies were uncontrolled. All 31 studies were rated fair quality (**Appendix D Tables 1-4**). Two studies analyzed data from the NCDB from 2004 to 2014,[202, 251] and two studies analyzed data from SEER from 2001 to 2009,[237, 241] likely resulting in some patient overlap in analyses. Four SBRT studies reported harms outcomes among subgroups defined by age, sex, and comorbidities.[204, 251, 255, 261]

The strength of evidence for harms from treatment of stage I NSCLC is moderate for surgical resection and low for SBRT/SABR. Estimates of low 30- and 90-day mortality rates are reasonably consistent and precise for surgical resection, as are the estimates for specific adverse effects. For SBRT/SABR, estimates for 30- and 90-day mortality are reasonably consistently low and for specific adverse events are consistently mild to moderate. However, a majority of the SBRT/SABR studies enrolled fewer than 200 patients (i.e., are imprecise) and are clinically heterogeneous in terms of patients and treatment details. Both bodies of evidence are primarily uncontrolled studies of fair quality and may be affected by selective reporting of specific adverse events.

Harms From Surgical Resection

Description of Included Studies

Twenty-five uncontrolled studies of mostly fair quality evaluated the harms of surgical resection for the treatment of stage I NSCLC between 1983 and 2015 and were included in KQ 7 (**Appendix E Tables 4** and **5**).[170, 173, 176, 177, 179, 182, 185, 189, 196, 237-252] Sample sizes ranged from 540 patients in a good-quality study conducted in the United Kingdom from 2011 to 2012[177] to 146,908 patients in an analysis of the NCDB from 2004 to 2013.[245] Most of the studies were conducted in the United States with the exceptions of one study from Denmark,[249] one from the United Kingdom,[177] and two from Japan.[173, 179] A total of 737,775 patients with stage I NSCLC were included in the 25 studies, but there is likely overlap of indeterminant extent of patients among studies that used data from the NCDB (k=9 studies)[189, 239, 240, 243-245, 250-252] and SEER databases (k=3).[237, 241, 247] The mean or median age ranged from 65 to 69 years in most studies. One good quality study, which enrolled only patients who received wedge resection, was

conducted among patients with a median age of 72 years (interquartile ratio [IQR]: 64 to 77 years).[177] Two studies of SEER data reported median ages of 75 years, but the entire patient population also included patients receiving SBRT (who tend to be older; see below).[237, 241] Ninety-six percent of the patients in the analysis of VINCI data (i.e., veterans) were male;[196] the remaining studies were relatively balanced between males and females (range of % male: 43% to 56%). While some studies focused solely on patients who received lobectomy,[173, 182, 185, 238, 247, 249, 250] most studies included multiple types of surgical resection including lobectomy, segmentectomy, wedge resection, and pneumonectomy.

Detailed Results

The 30-day mortality rates ranged from zero in a good-quality Japanese study of 618 clinical stage IA patients[179] to 3.6 percent (95% CI, 3.06% to 4.1%) in an analysis of almost 5,000 patients in the SEER database from 1992 to 2002 who were 65 years of age or older.[247] The 30-day mortality rate for 1,386 patients receiving a pneumonectomy (i.e., surgical removal of one lung) in the NCDB from 2004 to 2013 was an outlier at 7.8 percent compared with rates of 2 percent and 1.8 percent for lobectomy (i.e., removal of a single lobe) and SLR (i.e., removal of less than a full lobe, such as wedge resection or segmentectomy), respectively.[251] The 30-day mortality rate among patients in the NCDB who delayed surgery 8 or more weeks after diagnosis was higher (2.9%) than patients who did not delay surgery (2.4%, p=0.01).[240] One study in Denmark reported a higher 30-day mortality rate among lobectomy patients who received a thoracotomy (2.9%) than patients who received VATS (1.1%, p=0.02).[249] There were no significant differences among various surgical approaches in other studies.[176, 196, 237, 238, 248, 250] Ninety-day mortality rates ranged from 2 percent in a study of VATS vs. open lobectomy[182] to 4.8 percent (95% CI, 2.7% to 7.8%) among lobectomy patients in another study of lobectomy and segmentectomy.[176] The 90-day mortality rate for 1,386 patients receiving a pneumonectomy in the NCDB from 2004 to 2013 was another outlier at 11.9 percent compared with rates of 3.5 percent and 3.3 percent for lobectomy and SLR, respectively.[251] In an analysis of over 145,000 patients in the NCDB from 2004 to 2013, the 30- and 90-day mortality rates were significantly higher (but still <4%) among patients who did not meet quality measures that included anatomical resection, surgery within 8 weeks of diagnosis, resection for cure or complete remission, or sampling of 10 or more lymph nodes.[245]

The overall perioperative morbidity (categorized as pulmonary, cardiac, neurological, and renal, but not otherwise defined) in one study comparing VATS to open lobectomy among 963 patients was 19 percent and 34 percent, respectively (p=0.0001)[182] and in another study was 46 percent and 36 percent for patients (n=899) receiving lobectomy and segmentectomy, respectively (p=0.01) (**Appendix E Table 5**).[248] Less than 30 percent of patients experienced any perioperative morbidity in a study of 800 patients (28%)[170] or acute toxicity within 60 days of surgery in 1,183 patients in a National Comprehensive Cancer Network analysis (23%).[246] Rates of specific adverse events attributed to surgical resection were generally low. The percentage of patients experiencing infection or pneumonia ranged from 3.3 percent[238] to 7 percent;[182] patients with delayed surgery experienced significantly higher rates of infection (11%) than patients without delayed surgery (6%, p=0.006).[240] Patients undergoing delayed surgery,[240] VATS lobectomy (compared with robotic lobectomy[238] or segmentectomy[248]), or who were pathologic stage IB (compared with pathologic stage IA[173]) experienced higher blood loss (sometimes

defined by need for transfusion or a return to the operating room). Three studies reported rates of bronchopleural fistulas of less than 0.5 percent.[170, 182, 238] Greater than 10 percent of patients in some studies reported cardiac arrhythmias[170, 182, 238, 240, 242] or pulmonary morbidities,[182, 238, 240, 247, 248] including air leaks.[238, 240]

Subgroups

Five studies evaluated harms of surgical resection among subgroups of patients.[189, 239, 242, 248, 251] Thirty-day mortality rates increased with increasing age in four studies. Compared with patients under 75 years, patients 75 years or older were 165 percent more likely to die within 30 days of surgery (OR, 2.65, 95% CI, 2.38 to 2.95) in a multivariable analysis of NCDB data from 2003 to 2011.[239] In another NCDB analysis, the 30- and 90-day unadjusted mortality rates for patients 55 years or younger were 0.97 percent and 1.55 percent, respectively, compared with patients 80 years or older (3.94% and 7.30%, respectively).[251] Mortality rates were higher among males than females in two studies.[189, 239] Finally, the risk of death within 30 days of surgery increased as the Charleson-Deyo Comorbidity Score increased in two studies.[189, 239] One study found no difference in mortality between "normal"- and "high"-risk patients;[242] high-risk patients were primarily identified as having predicted forced expiratory volume in 1 second and predicted diffusion capacity of the lung for carbon monoxide of 50 percent or less.

Update Search Summary: Surgery Results

Four fair-quality studies[217, 220, 273, 274] identified through the update search evaluated harms of surgical resection for the treatment of stage I NSCLC between 2017 and 2018 and were included for KQ7 (**Appendix E Tables 7** and **8**). One study analyzed 6,905 patients from the Polish National Lung Cancer Registry from 2007 to 2013,[217] and another analyzed 9,508 patients from the SEER database from 2000 to 2009.[273] Estimates of 30- and 90-day mortality and perioperative morbidity (when reported) were reasonably consistent and precise, and they were similar to the original search yield's findings for surgical resection.

Harms From SBRT

Description of Included Studies

Thirty-one fair quality studies described in 32 articles evaluated SBRT/SABR (n=17,353 patients with stage I NSCLC)[196-198, 202-207, 237, 241, 246, 251, 254-272] for the treatment of stage I NSCLC between 1998 and 2015 and were included for KQ 7 (**Appendix E Tables 4** and **6**). Sample sizes ranged from 30 patients in a single institution study in Italy[262] to 8,216 in an analysis of the NCDB from 2004 to 2013;[275] most studies enrolled fewer than 200 patients. One of the studies was a fair-quality RCT comparing two dosing regimens of SBRT (34 Gy in one fraction vs. 48 Gy in four consecutive daily fractions);[263] the remaining studies were uncontrolled. While most studies were conducted in North America, there were a few conducted in Europe[203, 206, 207, 254, 256, 262, 267, 270] and Asia.[198, 205, 255, 268] The mean or median age of patients receiving SBRT/SABR was between 70 and 79, and the percentage of male patients ranged from 37 percent to 97 percent. Treatment-related toxicity and adverse events were evaluated using the Common Toxicity Criteria for Adverse Events version 3 or 4 in 18 studies. Adverse events were graded according

to severity (grade 1: mild; grade 2: moderate; grade 3: severe or medically significant; grade 4: life-threatening consequences; grade 5: death related to adverse event).[276] Clinical toxicities were also graded using Radiation Therapy Oncology Group (RTOG) criteria[277] in two studies.[262, 263]

Detailed Results

Nine studies reported 30-day mortality rates of 0 to 2 percent;[196, 198, 203, 237, 246, 251, 258, 265, 266] 90-day mortality rates were similar (range: 0% to 3%) in nine studies.[196, 198, 203, 237, 241, 251, 258, 265, 266] The most commonly reported adverse events were radiological toxicity, pulmonary toxicity and respiratory disorders, fatigue, pain, and dermatologic adverse events. The RCT comparing two SBRT dosing regimens reported that a majority of reported adverse events were grade 2 (i.e., moderate);[263] the incidence of grade 2 toxicities ranged from 9 percent[271] to 31 percent[206]in the other studies, and the common toxicities were dyspnea, esophageal pain, chest wall pain, and coughing. The range of grade 3 (i.e., severe) toxicities was 0 percent to 13 percent in 13 studies; the most common grade 3 toxicities reported were pulmonary toxicities, fatigue, chest wall pain, and dermatitis.[197, 203, 205, 206, 255, 260, 262-264, 268, 269, 271, 272] Seven studies reported no grade 4 (i.e., life threatening) adverse events.[197, 206, 207, 255, 264, 267, 269, 271] Among six studies that reported patients who experienced a grade 4 adverse event,[205, 207, 262, 263, 265, 268, 272] the highest incidence rate was 5 percent (dyspnea among patients with medically inoperable tumors)[268] and the most commonly reported toxicity was pulmonary in nature. One study reported a death due to hemoptysis in a patient older than 75 years of age,[204] and two studies each reported a single death due radiation pneumonitis.[256, 260]

Thirteen studies reported data related to rib fractures;[197, 204, 207, 254, 256, 258, 260, 261, 263, 264, 267, 268, 271] most were grade 1 (i.e., mild) or 2 (i.e., moderate) according to the Common Toxicity Criteria for Adverse Events or RTOG criteria. The overall incidence of any rib fracture ranged from 0[271] to 37 percent.[261] In the study reporting the highest overall incidence, 17 of 46 patients reported 41 fractured ribs and the median time to a fractured rib after SBRT was 21 months (range: 7 to 40 months).[261] In the RCT comparing dosing regimens, 18 percent of patients receiving 34 Gy in one fraction and only 2 percent of patients receiving 48 Gy in four fractions at 12 Gy per fraction experienced an "injury" that included fracture.[263] Nineteen studies reported data related to radiation pneumonitis.[197, 204, 205, 207, 237, 246, 254-256, 258-260, 263, 264, 266, 267, 270-272] As many as 75% of patients experienced grade 1 radiation pneumonitis[197] and as described above, only two patients experienced grade 5 (i.e., fatal) radiation pneumonitis.[256, 260] The rate of grade 2, 3, or 4 (i.e., moderate severity to life-threatening) radiation pneumonitis in all of the studies was less than 12 percent.

Subgroups

Four SBRT studies reported harms outcomes among subgroups defined by age, sex, and comorbidities.[204, 251, 255, 261] Thirty- and 90-day unadjusted mortality rates did not substantially differ by age in one study of over 8,000 patients in the NCDB,[251] and rates of grade 2 or 3 (i.e., moderate or severe) adverse events did not differ by age (<75 years, ≥75 years) in a study of 772 U.S.-based patients.[204] In one Japanese study, females experienced numerically higher rates of grade 2 or higher radiation pneumonitis than males (16% vs. 13%, respectively; adjusted OR 1.30 [95% CI, 0.53 to 3.10]).[255] In a small study of 46 patients, females were significantly more

likely to experience rib fractures (adjusted OR 4.43), but the CI was very wide (1.68 to 11.69).[261] In that same study, patients with diabetes or COPD were less likely to experience rib fractures (OR 0.51 [95% CI, 0.09 to 2.88) for diabetes and OR 0.97 [95% CI, 0.28 to 3.39] for COPD) but not significantly so.[261]

Update Search Summary: SBRT Results

Twenty-nine studies (28 fair-quality studies[224-230, 232-234, 236, 278-295] and 1 good-quality study[236]) identified through the update search evaluated the effectiveness of SBRT for the treatment of stage I NSCLC between 2006 and 2019 (**Appendix E Tables 7** and **9**). Two studies analyzed 27,795 patients from the NCDB from 2004 to 2014,[228, 232] one analyzed 99 patients from the Amsterdam Cancer Registry from 2002 to 2007,[289] one study analyzed 55 patients from the RTOG 0236 uncontrolled clinical trial,[279] and one RCT (the CHISEL trial) analyzed 66 patients.[293] Estimates of 30- and 90-day mortality from the update search yield were reasonably consistently low and for specific adverse events were consistently mild to moderate. The most commonly reported adverse events were radiological toxicity, pulmonary toxicity and respiratory disorders, fatigue, chest wall pain, and dermatologic adverse events. These findings matched those of the original search yield, and studies from the update search yield were subject to the same limitations. Studies identified in the update search did not report enough information to determine whether most included patients experienced adverse events.

Key Question 8. What Is the Magnitude of Change in All-Cause and Lung Cancer Mortality That Results From a Specified Change in Lung Cancer Incidence (and Change in Distribution of Lung Cancer Stages [i.e., Stage Shift]) After Screening?

The NLST results indicate that an absolute increase in lung cancer incidence of 0.5 percent (4.1% vs. 3.6% of participants) and the associated absolute increase in Stage I lung cancers of 19 percent (50% vs. 31% of incident lung cancers) and absolute decrease in Stage IV lung cancers of 14 percent (22% vs. 36% of incident lung cancers) after three annual rounds of screening with LDCT (compared with CXR) were associated with 52 fewer lung cancer deaths and 84 fewer all-cause deaths per 100,000 person-years.[32, 63] Attributing the changes in lung cancer and all-cause mortality to this particular change in lung cancer incidence assumes the approach to workup of lung cancers and subsequent treatments (surgical interventions) used in the NLST.

The NELSON results indicate that an absolute increase in lung cancer incidence of 0.6 percent (5.2% vs. 4.6% of participants) and the associated absolute increase in Stage I lung cancers of 27 percent (41% vs. 14% of incident lung cancers) and absolute decrease in Stage IV lung cancers of 19 percent (27% vs. 46% of incident lung cancers) after four rounds of screening with LDCT using a volumetric method (compared with no screening) were associated with 83 fewer lung cancer deaths per 100,000 person-years, but not fewer all-cause deaths.[76] Attributing the changes in lung cancer to this particular change in lung cancer incidence assumes the approach to workup of lung cancers and subsequent treatments (surgical interventions) used in NELSON.

Chapter 4. Discussion

Summary of Evidence

Table 11 provides a summary of the main findings in this evidence review organized by KQ along with a description of consistency, precision, quality, limitations, strength of evidence, and applicability.

Evidence for Benefit and Harms of Screening

For benefits of screening, the good-quality NLST demonstrated a reduction in lung cancer mortality and all-cause mortality with three rounds of annual LDCT screening compared with CXR. Its results indicate an NNS of 323 to prevent one lung cancer death over 6.5 years of followup. The fair-quality NELSON trial also demonstrated a reduction in lung cancer mortality, but not all-cause mortality, with four rounds of LDCT screening with increasing intervals; its results indicate a NNS of 130 to prevent one lung cancer death over 10 years of followup. Harms of screening include false-positive results leading to unnecessary tests and invasive procedures, overdiagnosis, incidental findings, short-term increases in distress because of indeterminate results, and, rarely, radiation-induced cancer (estimated 0.26 to 0.81 major cancers for every 1,000 people screened with 10 annual LDCTs). For every 1,000 persons screened in the NLST, false-positive results led to 17 invasive procedures. Overdiagnosis estimates ranged from a 0 to 67 percent chance that a screen-detected lung cancer was overdiagnosed. The NLST data indicate approximately four cases of overdiagnosis (and 3 lung cancer deaths prevented) per 1,000 people screened (for 3 rounds of annual screening and 6.5 years of followup). Incidental findings were common and variably defined with a wide range reported across studies (4.4% to 40.7%). Common incidental findings were coronary artery calcification; aortic aneurysms; emphysema; infectious and inflammatory processes; and masses, nodules, or cysts of the kidney, breast, adrenal, liver, thyroid, pancreas, spine, and lymph nodes. Incidental findings led to consultations, additional imaging, and invasive procedures. To further underscore the downstream impact of incidental findings, a study of patients undergoing one round of LDCT screening in the Cleveland Clinic screening program estimated a 1-year cost of screening based on Medicare reimbursement of $817 per patient, of which 46 percent was attributed to evaluation and treatment of incidental findings.[167]

The NLST and NELSON results are generally applicable to high-risk current and former smokers ages 50 to 74 years, but participants were younger, more highly educated, less likely to be current smokers than the U.S. screening-eligible population, and had limited racial and ethnic diversity (91% white; <5% black; <2% Hispanic or Latino). The general U.S. population eligible for lung cancer screening may be less likely to benefit from early detection compared with the NLST and NELSON participants because they face a high risk of death from competing causes, such as heart disease, diabetes, or stroke.[25] A study using data from the 2012 Health and Retirement Study (a national survey of adults 50 years or older) evaluated comorbidities, life expectancy, smoking history, and other characteristics in the screening-eligible population and in NLST participants; it reported a lower 5-year survival rate and life expectancy in the screening-

eligible persons compared with NLST participants (87% vs. 93%, p<0.001 and 18.7 years vs. 21.2 years, respectively).[25] NELSON did not allow people with any of the following to be enrolled in the trial: moderate or severe health problems and an inability to climb two flights of stairs; weight over 140 kg; or current or past renal cancer, melanoma, or breast cancer.
The NLST was mainly conducted at large academic centers, potentially limiting its applicability to community-based practice (e.g., because of challenges with implementation [Contextual Question 1 in **Appendix A**], level of multidisciplinary expertise). Many of the trial centers are well recognized for expertise in thoracic radiology as well as cancer diagnosis and treatment.[32] Community centers may be less equipped for screening programs and for treatment of lung cancers identified by screening. For example, the NLST publication noted that mortality associated with surgical resection of lung cancer was much lower in the trial than that reported for the U.S. population (1% vs. 4%).[32, 296]

Regarding pack-years of smoking among trial participants, NLST required a minimum of 30 pack-years for enrollment, whereas NELSON had a lower threshold for eligibility. Specifically, it required that participants smoked either (1) more than 15 cigarettes a day for more than 25 years or (2) more than 10 cigarettes a day for over 30 years, which roughly translate to about 19 pack-years and 15 pack-years, respectively. Among participants enrolled in the study, the median number of pack-years smoked was 38 (interquartile ratio 29.7 to 49.5). The trials enrolled current smokers or those who had quit within 10 years (NELSON) or 15 years (NLST).
Most studies reviewed in this report (including NLST) did not use current nodule evaluation protocols such as Lung-RADS (endorsed by the American College of Radiology). A study included in this review estimated that Lung-RADS would reduce false-positive results compared with NLST criteria and that about 23 percent of all invasive procedures for false-positive results from the NLST would have been prevented by using Lung-RADS criteria.[100] A recent publication developed an infographic to show the outcomes of screening 1,000 persons (with 3 annual screens) if Lung-RADS had been used in the NLST:[297]

- 779 persons would have normal results
- 180 persons would have at least one abnormal result requiring a followup LDCT at 3 or 6 months but no lung cancer diagnosis (false-positive screens)
  - 13 of those 180 would require an invasive procedure to rule out lung cancer
  - 0.4 (1 in 2,500 screened) would have a major complication from an invasive procedure
  - 0.2 (1 in 5,000 screened) would die within 60 days of an invasive procedure from any cause
- 41 persons would be diagnosed with lung cancer
  - 4 cases represent overdiagnosis
  - 3 cases represent lung cancer deaths prevented because of screening

The infographic did not address some important harms, including those from incidental findings. Application of lung cancer screening with (1) current nodule management protocols and (2) the use of risk prediction models might improve the balance of benefits and harms, although the strength of evidence supporting this possibility was low. There remains considerable uncertainty about how such approaches would perform in actual practice because the evidence was largely derived from post hoc application of criteria to trial data (for Lung-RADS) and from modeling

studies (for risk prediction) and does not include prospective clinical utility studies. When applied to current clinical practice, lung cancer screening programs have demonstrated significant variation, even within a single institution type (e.g., the Veterans Health Administration demonstration project reported a wide range of false-positive rates [12.6% to 45.8% of veterans eligible for screening] and incidental findings deemed likely to need followup [20.0% to 63.4%] across eight study sites).[38]

Risk prediction models are an alternative to risk factor–based selection of participants for lung cancer screening and aim to improve identification of those most likely to benefit and to avoid screening those least likely to develop and die from lung cancer. Several models have been developed that incorporate multiple risk factors into regression-based models that predict an absolute risk of lung cancer incidence or mortality. Subjects meeting a specified risk threshold could be offered screening.

The 2013 USPSTF recommendations for lung cancer screening identify subjects appropriate for screening using risk factors of age and smoking history. Some studies suggested that even among persons meeting these criteria there is a broad range of risk of lung cancer incidence and mortality. An analysis of NLST data reported that about 90 percent of the mortality benefit was achieved by screening the highest 60th percentile at risk.[56] Additionally, some studies have noted that persons not meeting USPSTF criteria (due to age or lower cumulative pack-years) may benefit from lung cancer screening, in part due to loss of information from dichotomizing smoking history and not accounting for other known risk factors for lung cancer such as African American race, COPD, radiation treatment, family history, and occupational exposures.[298, 299]

Studies included in this evidence review found that risk prediction models increased the number of screen-preventable deaths. In most cases, they also reduced the number of participants needed to screen to prevent one lung cancer death (i.e., increased efficiency of screening), and reduced the number of false-positive selections for screening per prevented lung cancer death compared with risk factor–based screening, when NLST-like cancer detection and mortality reductions were assumed. The exception is one study of the PLCOm2012 model applied to a more contemporary cohort (NHIS 2015) where risk thresholds of 1.3 percent and 1.51 percent result in a higher NNS and number of false-positive selections for screening per prevented death.[89] These risk thresholds were developed using the PLCO study, which enrolled patients from 1993 to 2001. The number of smokers in the United States has decreased since that time, which is reflected in the NHIS dataset, suggesting fixed population methods can lead to different thresholds across different cohorts due to underlying differences in patient demographics, smoking behavior, and other risk factors. Overall, the results of the risk prediction studies suggest that lung cancer screening benefits may be improved and harms might be reduced if participants could be selected based on risk prediction calculations,[56, 84, 85] with re-evaluation of risk thresholds over time.

The studies comparing risk prediction model–guided screening with risk factor–based screening have limitations. First, studies reporting increased screen-preventable deaths and reduced NNS with risk prediction models assumed NLST-like benefits from screening to estimate outcomes.[84, 85] Related to the aforementioned applicability issues, lung cancer screening in routine clinical practice and screening that targets persons who would not have been eligible for the NLST may

not result in similar detection of screen-preventable cancers and mortality benefits as found in the trial. Second, no studies included in this systematic review evaluated life-years gained by using risk prediction models; only screen-prevented deaths were reported. At older ages, while screening may increase the number of deaths averted, the competing risk of death from other conditions may attenuate improvements in life-years gained. The collaborative decision analysis that is being conducted for the USPSTF addresses this issue. Third, almost all risk prediction models were studied by retrospectively applying models to previously conducted cohort studies or trials.

An important challenge related to the use and evaluation of risk prediction models is the lack of established risk thresholds to implement individualized risk prediction–based screening in practice. The decision to offer LDCT screening to an individual would be contingent on whether the absolute risk of lung cancer incidence or mortality falls above a prespecified cut-off. The included studies used a variety of approaches to estimating risk thresholds, most commonly a USPSTF- or NLST-fixed population screening size. With this approach, the risk threshold is set where the same number of persons would undergo LDCT as those who would be identified by a risk factor–based approach, implying that the absolute number of participants screened by USPSTF criteria is considered an acceptable number of persons to screen.

Another approach was to determine the risk threshold above which there was evidence of mortality benefit from the NLST trial. Two studies of the PLCOm2012 models using this risk threshold (≥1.51%) reported the number of false-positive selections for screening and specificities from which rates of false-positive selections were calculated. It is important to note that "false positive" for KQ 2 refers to the model performance with respect to the models selecting persons to be screened who did not have or develop lung cancer events (diagnosis or death), not with respect to LDCT results. While the overall percentage of false-positive selections for screening was similar for risk prediction model- and risk factor–based screening approaches, the PLCOm2012 model had a lower rate of false-positive selections than the USPSTF criteria in the U.S.-based PLCO cohort (33.8% vs. 37.3%) compared with an Australian study in which the model has a higher rate of false-positive selections vs. USPSTF criteria (28.0% vs. 23.7%). A greater percentage of the U.S. study had a 6-year lung cancer incidence ≥1.51% than the Australian study (35% vs. 25%), suggesting that the underlying risk of the population may affect evaluation of the model and model performance in different populations.

The accompanying decision analysis evaluates three risk prediction models captured by the systematic review that are publicly available and accessible: the PLCOm2012, LCDRAT, and Bach models.[300] The decision analysis uses simplified versions of all three of these models restricted to age, sex, and smoking covariates because jointly simulating other risk factors (e.g., race/ethnicity, family history, medical comorbidities) was not possible due to the lack of well-calibrated and validated lung cancer natural history models incorporating all covariates, accounting for their correlation and time trends. While the CISNET group has extended the Smoking History Generator to consider other covariates, the new Risk Factor Generator is still being evaluated and validated.

Accuracy of Screening With LDCT

The previous evidence review for the USPSTF included one trial and five cohort studies reporting sensitivity (from 80 to 100%) and two trials and five cohort studies reporting specificity (from 28 to 100%).[46] This review includes the studies from the prior review in addition to more recently published studies. In this review, the vast majority of studies reported sensitivity over 80 percent and specificity over 75 percent. NPVs were universally high (range: 97.7% to 100%), but PPVs showed more variation across studies (range: 3.3% to 43.5%). Variability in accuracy was mainly attributed to heterogeneity of eligibility criteria, screening protocols (e.g., number of screening rounds, screening intervals), heterogeneity and completeness of followup length (e.g., to identify false-negative screens), and heterogeneity in the definitions (e.g., of positive tests, indeterminate tests, false-positive test, false-negative tests). Some studies focused on the number of positive scans or nodules rather than on the number of participants with a positive scan, making it challenging to calculate accuracy metrics.

Few studies used the nodule classification approach recommended by American College of Radiology (i.e., Lung-RADS). Studies comparing various approaches to nodule classification reported that using Lung-RADS in the NLST would have increased specificity while decreasing sensitivity and that increases in PPV are seen with increasing nodule size thresholds. The included studies provide limited evidence on whether volumetric or nonvolumetric approaches yield greater accuracy because there are no direct comparisons of these approaches; differences in study populations (e.g., lung cancer incidence) and other contributors to heterogeneity across studies may account for the higher PPVs that tend to be reported in studies using volumetric approaches.

Benefits and Harms of Surgery and SBRT for Stage I NSCLC

The effectiveness of screening for lung cancer with LDCT relies on identification of Stage I NSCLC and subsequent successful surgical removal. This review found a range of 5-year OS across studies from 33 to 86 percent for Stage I NSCLC. The included studies indicate that OS may be higher for lobectomy than SLR surgical approaches; Stage IA than Stage IB tumors; smaller than larger tumors; and for patients who are female, younger, nonsmokers, or have fewer comorbidities than patients who are male, older, smokers, or sicker. Harms of surgery include mortality (30-day mortality rates: 4% or less in most studies; 90-day mortality: 2% to 5% in most studies). Less than one-third of patients in most studies experienced treatment-related adverse events. Common adverse events included pulmonary events (e.g., air leak, pleural effusion) and cardiac arrhythmias.

Across the included studies there was substantial clinical heterogeneity of factors that are related to outcomes. NSCLC staging has changed over time (including definition of Stage I and tumor size criteria) and varied across studies, and studies varied in use of clinical or pathologic requirements for eligibility (i.e., some identified/enrolled participants based on clinical staging and others based on pathologic staging). Among studies that collected data on both clinical and pathologic staging, some upstaging after surgical resection often occurred (e.g., 20% of patients were upstaged in SEER[196]). Variation in surgical approaches over time may also be associated with patient outcomes, with worse outcomes for open surgery than for minimally invasive

approaches such as VATS resection. Use of lobectomy vs. limited/sublobar resection may be associated with patient outcomes, but patients who receive limited resections are often older and sicker.

SBRT is an emerging treatment technology that has not yet been standardized in terms of treatment protocols related to dose, frequency, and duration. Studies reported a wide range of 5-year OS (from 20% to 80%) and harms. Harms included 30- and 90-day mortality (rates ranged from 0% to 3%), pulmonary toxicities, respiratory disorders (including dyspnea), chest wall pain, fatigue, dermatologic reactions, rib fractures, and others. Adverse events were experienced by a majority of those treated with SBRT, but most were of mild or moderate severity. Variation in 5-year OS was likely related to clinical characteristics, such as age, comorbidities, and operability of tumors.

Limitations of the SBRT evidence include small sample sizes, often reporting only short-term survival outcomes (e.g., 2- or 3-year OS), lack of pathologic confirmation of lung cancer diagnosis and stage, and lack of comparison groups. Some studies of SBRT that were included for KQ 7 (harms) were excluded from KQ 6 because they only reported survival outcomes at timepoints less than 5 years.[237, 241, 254-258, 260, 263, 264, 266-268, 271, 272] We excluded additional short-term studies that would have been eligible for KQ 6 if they had longer followup; these studies were not eligible for KQ 7 either (because they did not report on harms).[301-313] Regarding pathologic confirmation of diagnosis and stage, it was often lacking in studies of SBRT because patients had not undergone surgical resection.

The evidence summarized in this review for surgery and SBRT generally comes from uncontrolled studies. No RCTs compared surgical resection with SBRT (the STARs, ROSEL, and ROG 1021 RCTs were all stopped early due to poor accrual). Investigators acknowledged how difficult it is to compare surgical resection with SBRT, primarily because SBRT was typically performed when surgery was contraindicated, and many performed propensity-score matched analyses. We did not include the evidence from comparative analyses, however, because it was beyond the scope of this review and instead reported on the absolute rates for eligible outcomes reported by the studies, which are not necessarily comparable across groups or studies.

Limitations

This review has limitations. The limitations of the included studies are discussed above in Results and Discussion. Here we focus on limitations of this review. We excluded non-English language articles. We excluded studies with sample size less than 500 or 1,000 for some KQs to focus on the best evidence. Doing so omitted some smaller studies that reported on harms of screening. For example, a study of 351 participants in the NELSON trial examined discomfort of LDCT scanning and waiting for the LDCT results.[314] Most participants (88% to 99%) reported experiencing no discomfort related to the LDCT scan, but about half reported at least some discomfort from waiting for the result (46%) and dreading the result (51%).

The KQ on risk prediction models (KQ 2) was focused on how well risk prediction models perform vs. current recommended risk factor–based criteria for lung cancer screening, with respect to estimated screen-preventable deaths or all-cause mortality, screening effectiveness (e.g., number needed to screen), and screening harms (e.g., false-positive screens). To be included in this review, a risk prediction model was required to be externally validated, include known lung cancer risk factors of age and smoking history, and compare outcomes with either USPSTF or screening criteria from a trial showing benefit (e.g., NLST). KQ 2 complements the decision analysis report[300] by evaluating previously published studies that apply risk prediction models to cohorts or representative samples of the U.S. population rather than simulated populations.

For accuracy, some included studies did not report accuracy metrics; rather, when sufficient data were reported, we calculated sensitivity, specificity, PPV, and NPV from the study data. This approach introduces uncertainty into these statistics and may account for variability (e.g., because it was sometimes uncertain whether data were number of nodules, number of LDCTs, or number of people).

Future Research Needs

The NLST and NELSON used different approaches to screening (for both screening intervals and definitions of positive tests). Additional research evaluating effectiveness and implementation of the volumetric approach used in NELSON vs. the approach used in the NLST, Lung-RADS, and other nodule management approaches could be useful to inform screening programs.

The optimal screening intervals for LDCT screening and optimal ages to start and stop screening could be important areas of future research. No good- or fair-quality trials directly compared different screening intervals. The 2013 USPSTF recommendation to screen every year from age 55 to 80 for everyone who meets risk-based criteria is relatively intensive. Longer intervals between LDCTs could be considered (e.g., perhaps longer intervals or stopping completely after some number of normal scans). The NELSON trial provides some empirical evidence of lung cancer mortality benefit with a less than annual screening interval.

Studies on how current nodule management approaches and risk prediction performs in clinical practice are needed. Possible next steps in evaluating risk prediction models for lung cancer screening include prospective evaluation compared with risk factor–based criteria, further research into appropriate risk thresholds, and implementation studies of lung cancer risk prediction models in clinical practice. The recently published CHEST guidelines on lung cancer screening noted that it is uncertain whether applying risk prediction models would lead to changes in patient or cancer phenotype that would affect the balance of benefits and harms of screening because the risk models include variables that affect nodule presence, risk of nodule evaluation, risk of lung cancer treatment, survival after lung cancer treatment, and overall survival.[315]

Research into biomarkers combined with LDCT could potentially improve the efficiency of lung cancer screening. Biomarkers related to detection of lung cancer could include protein antigens or antibodies, cell-free DNA, mRNA, and miRNA (noncoding RNA that regulates translation or degradation).[26] Biomarkers could potentially be used to identify high-risk candidates for screening with LDCT, as is currently under study in the Early Cancer detection test-Lung cancer Scotland (ECLS) study.[316] Biomarkers are in early stages of development, with work being done on evaluating the ability of biomarkers to discriminate between persons with and without the disease, rather than prospectively detecting persons with early disease.[26]

Three ongoing trials conducted in Japan, China, and the United Kingdom were identified in this review.[117, 317, 318] The Japanese randomized trial for evaluating the efficacy of low-dose thoracic CT screening for lung cancer in people with a smoking history of less than 30 pack-years (JECS study) plans to include 17,500 subjects in each arm.[317] Participants will be randomized to LDCT in Years 1 and 6 or to CXR in Year 1. Participants in both arms are also encouraged to have annual CXR for lung cancer screening. The primary outcomes are the sensitivity and specificity of the screening modalities in the first year, and secondary outcomes include the lung cancer stage and incidence, harms of screening, and mortality over 10 years. An RCT in China randomized 6,717 participants with at least 20 pack-years of smoking to LDCT screening every 2 years for three rounds or to standard care.[318] The primary aim is to evaluate detection of lung cancer, and the secondary aim is to evaluate lung cancer–specific mortality. The UKLS pilot randomized 4,055 people; the full trial is expected to randomize another 28,000 participants from seven centers.[117] Enrollment into UKLS was based on a risk questionnaire (Liverpool Lung Project risk model version 2) for people 50 to 75 years of age, to identify those at high risk of developing lung cancer (≥5% over 5 years). Although the UKLS has reported some preliminary findings from its pilot phase that are described in this evidence report (e.g., for accuracy, false-positive results, and possible psychosocial harms), assessment of health and mortality outcomes is ongoing and will be reported after followup of 10 years.

Conclusion

Screening high-risk persons with LDCT can reduce lung cancer mortality and may reduce all-cause mortality, but it also causes false-positive results leading to unnecessary tests and invasive procedures, overdiagnosis, incidental findings, short-term increases in distress (from indeterminate results), and, rarely, radiation-induced cancers. The evidence for benefits comes from two RCTs that enrolled participants who were more likely to benefit than the U.S. screening-eligible population and that were mainly conducted at large academic centers, potentially limiting applicability to community-based practice. Application of lung cancer screening with current nodule management protocols (e.g., Lung-RADS) might improve the balance of benefits and harms. Use of risk prediction models might improve the balance of benefits and harms, although there remains considerable uncertainty about how such approaches would perform in actual practice because current evidence does not include prospective clinical utility studies.

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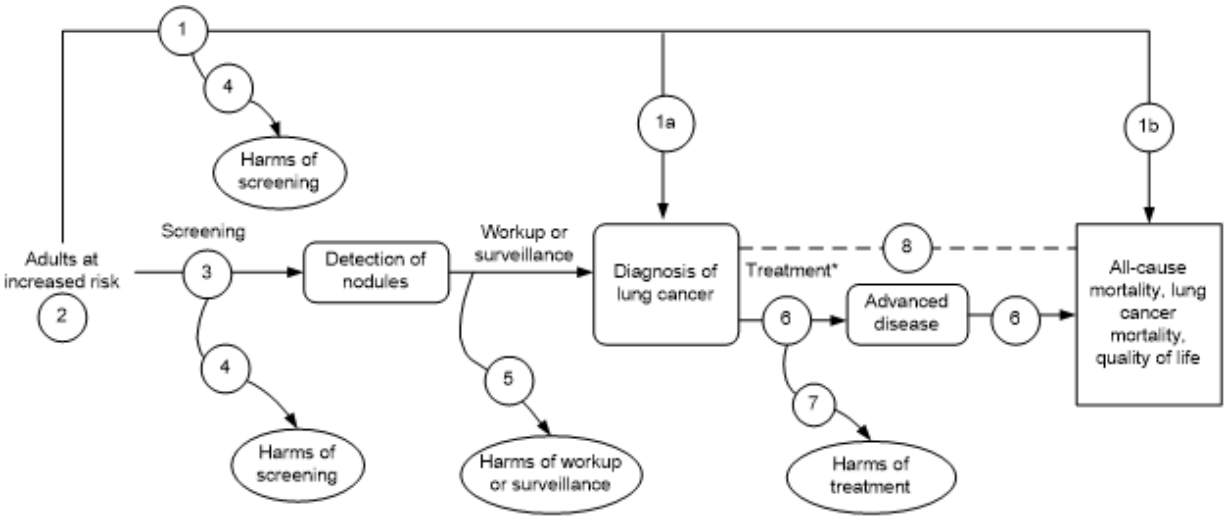
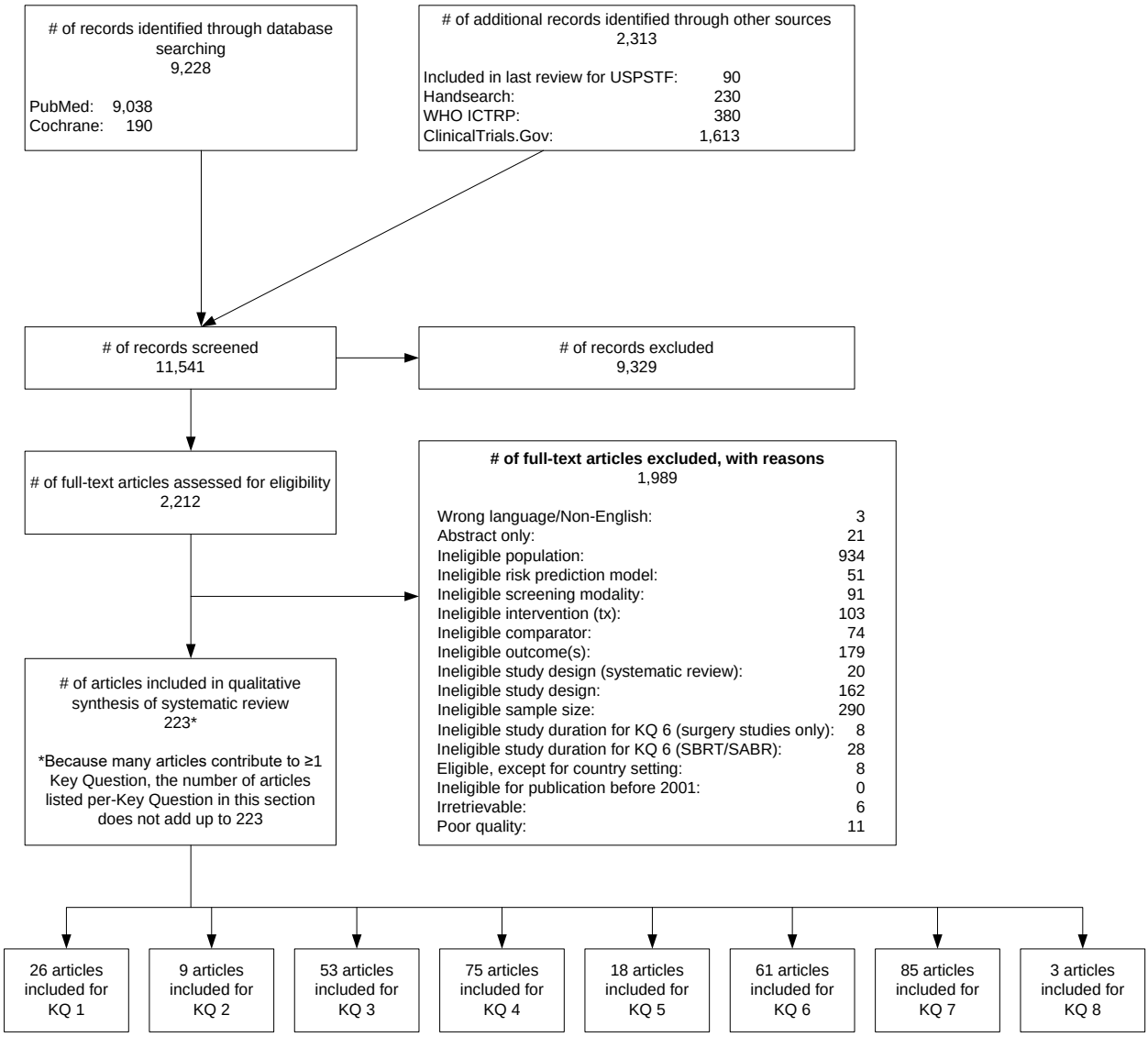
Figure 1. Analytic Framework



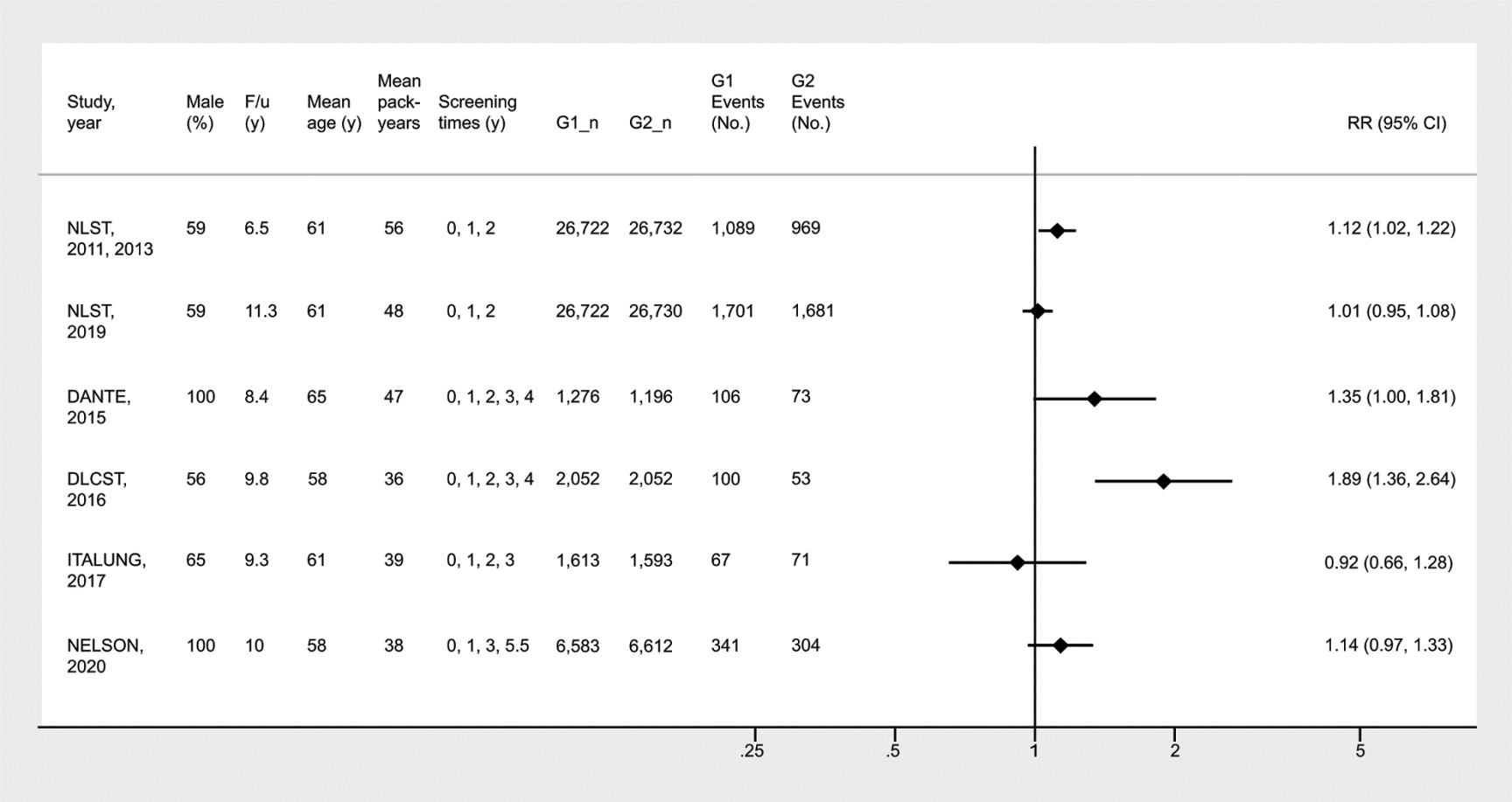
* The evaluation of evidence on treatment was limited to studies of surgical resection or stereotactic body radiotherapy for stage I NSCLC.
Abbreviations: NSCLC=non-small cell lung cancer.

Figure 2. Summary of Evidence Search and Selection



Abbreviations: KQ=key question; SBRT/SABR=SBRT=stereotactic body radiotherapy/SABR= stereotactic ablative radiation.

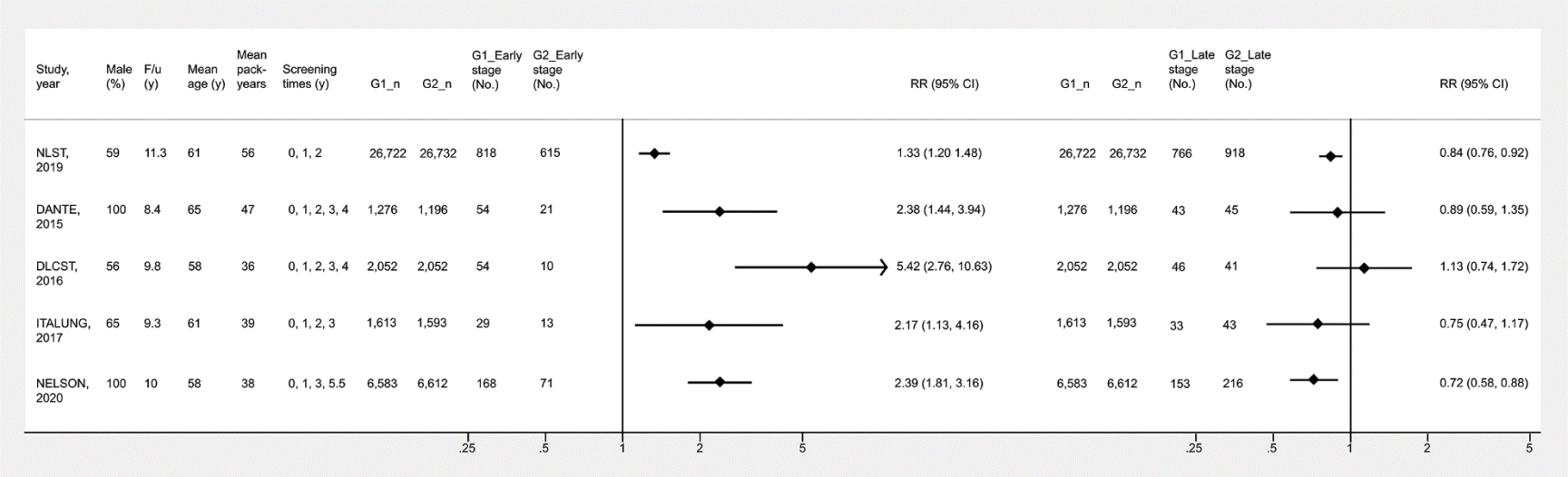
Figure 3. Trial Results for Lung Cancer Incidence (KQ 1)



Note: G1=LDCT; G2=Control; Favors Intervention indicates fewer incident lung cancers with intervention (LDCT screening); Favors Control indicates more incident lung cancers with intervention. Two rows are included in the figure for the NLST, showing the data from the 6.5-year followup and from the extended post-screening followup data at a median of 11.3 years after randomization for lung cancer incidence. The NELSON trial reported lung cancer incidence for the 13,195 males enrolled in the trial, excluding the 2,594 females that were enrolled. Therefore, the NELSON results in the figure above include only data for male participants (data were not reported for the female participants). The trial did not report total person-years of followup for lung cancer incidence, but those were able to be calculated from other data that were reported (5.58 cases per 1,000 person-years vs. 4.91 cases per 1,000 person-years at 10 years; RR, 1.14 [95% CI, 0.97, 1.33]).The Nelson trial reported median age and median pack-years instead of mean age and mean pack years. The LUSI trial was not included in the figure above because it did not reporting person-years of followup. The LUSI trial reported 85 lung cancers in the intervention group and 67 in the control group at a mean of 8.8 years follow up (p=0.16).

Abbreviations: DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=Italian Lung Cancer Screening Trial; LUSI=Lung cancer Screening Intervention; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial.

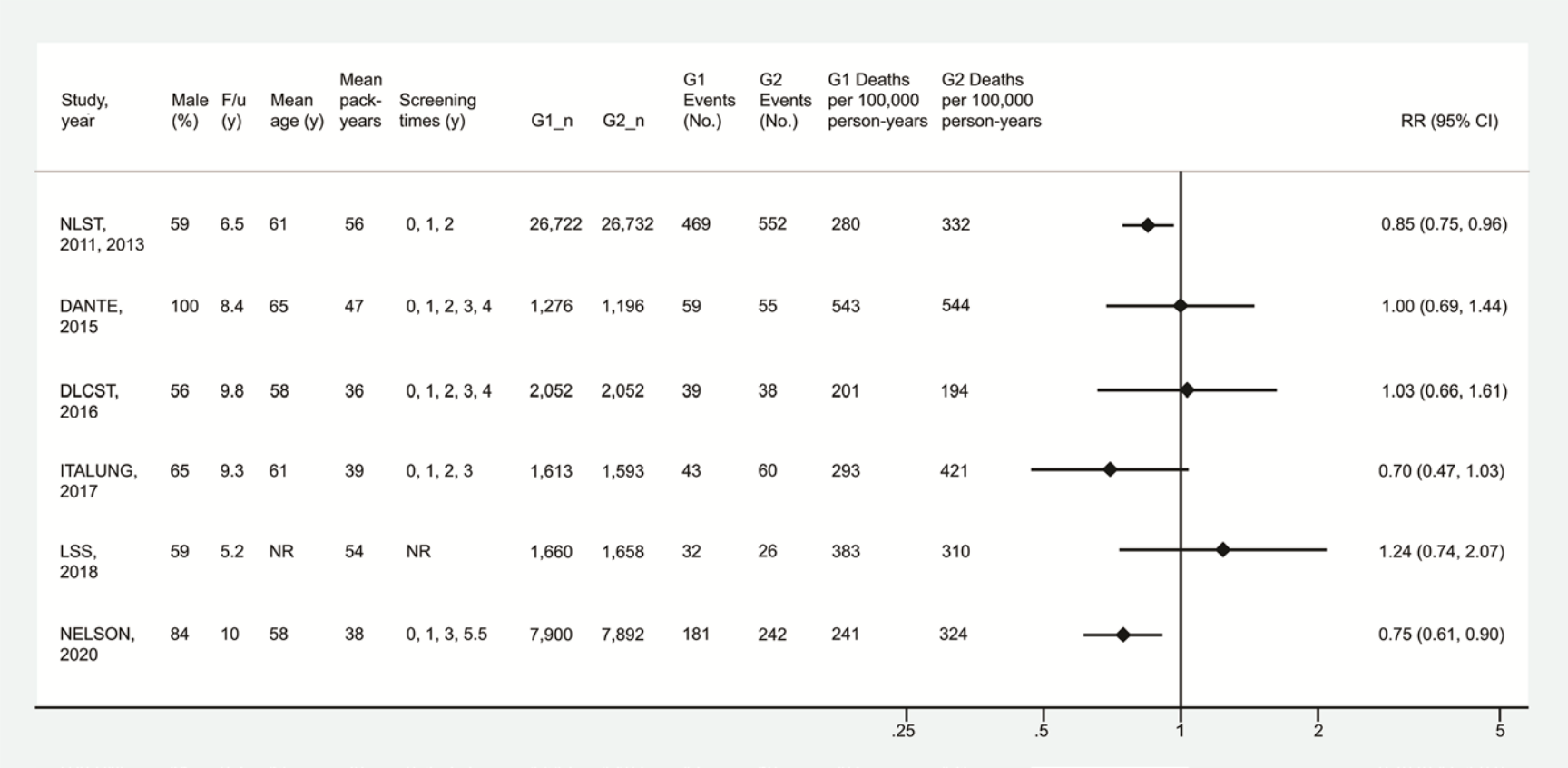
Figure 4. Trial Results for Incidence of Early (I-II) and Late (III-IV) Stage Lung Cancer (KQ 1)



Note: G1=LDCT; G2=Control; The MILD trial randomized participants to annual screening, biennial screening, or a control group. For the 10-year followup, the annual and biennial screening groups were combined. At the 10-year followup, the median duration of screening for those in the screening groups was 6.2 years.

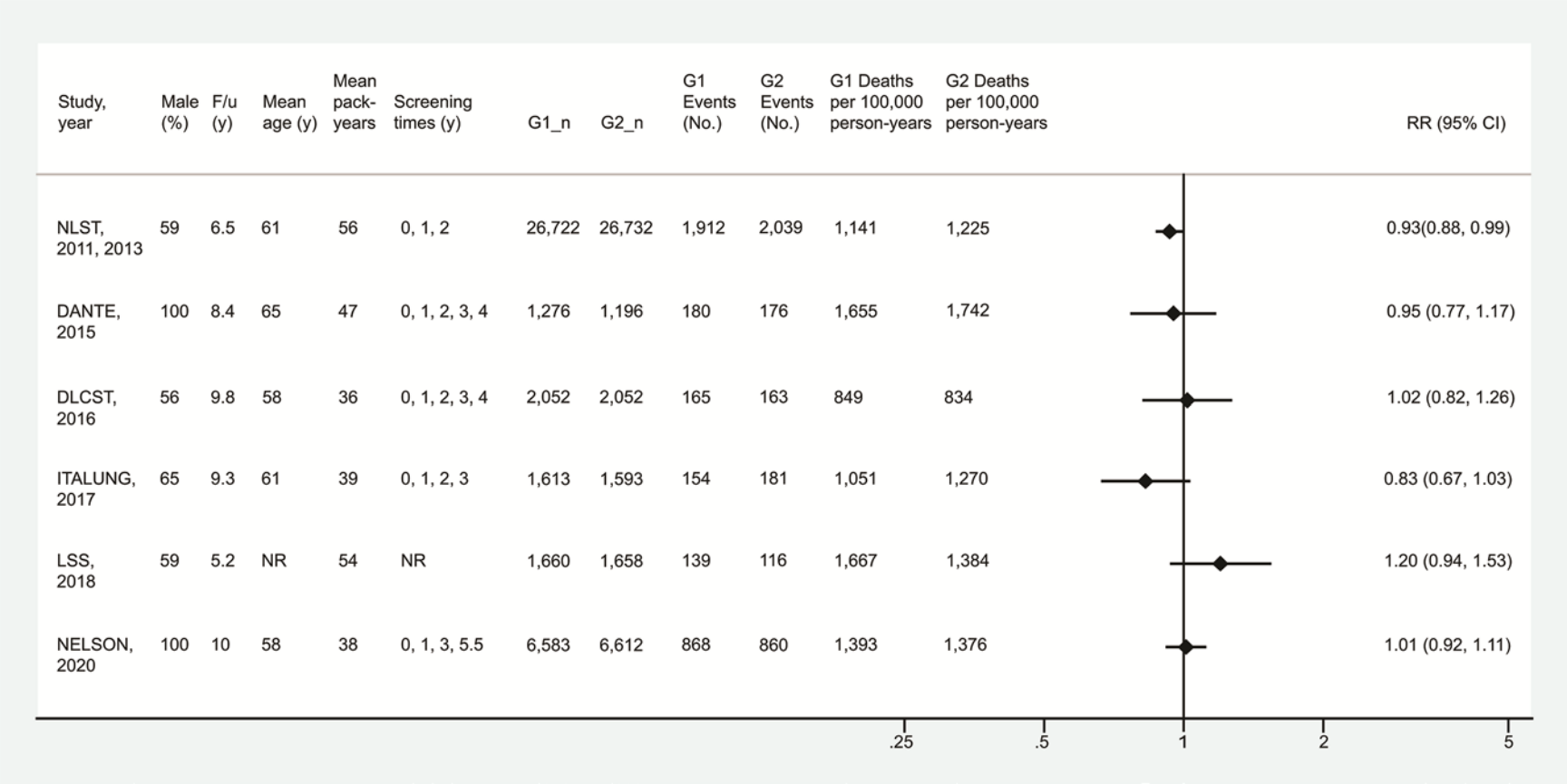
Abbreviations: DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=Italian Lung Cancer Screening Trial; MILD=Multicentric Italian Lung Detection; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial.

Figure 5. Trial Results for Lung Cancer Mortality (KQ 1)



Note: G1=LDCT; G2=Control. The NLST trial reported extended post-screening followup data at 12.3 years after randomization (not included in the figure above because person-years of followup were not reported): 1,147 lung cancer deaths occurred in the LDCT screening group (42.9 cases per 1,000 participants) and 1236 occurred in the CXR control group (46.2 cases per 1,000 participants) (RR, 0.92 [95% CI, 0.85, 1.00] and absolute difference between groups of 3.3 [95% CI, -0.2, 6.8] lung cancer deaths per 1,000 participants). The ITALUNG and LSS trials reported median pack per years instead of mean pack per years. The NELSON trial reported its main results for the 13,195 males enrolled in the trial (excluding the females enrolled), reporting 156 lung cancer deaths in the screening group and 206 lung cancer deaths in the control group for males at 10 years of followup (rate ratio 0.76 [95% CI, 0.61 to 0.94]). For the 2,594 females, NELSON reported 25 lung cancer deaths in the screening group and 36 in the control group at 10 years of followup (rate ratio 0.67 [95% CI, 0.38 to 1.14]). The NELSON results in the figure above combine data for all participants in the trial. The Nelson trial reported median age and median pack-years instead of mean age and mean pack-years. The LUSI trial was not included in the figure above because it did not report person-years of followup. The study reported 29 lung cancer deaths in the intervention group and 40 lung cancer deaths in the control group at a mean of 8.8 years follow up (p=0.19).
Abbreviations: DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=Italian Lung Cancer Screening Trial; LSS=Lung Screening Study; LUSI=Lung cancer Screening Intervention; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial.

Figure 6. Trial Results for All-Cause Mortality (KQ 1)



Note: G1=LDCT; G2=Control. The NLST trial reported extended post-screening followup data at 12.3 years after randomization (not included in the figure above because person-years of followup were not reported): 5,253 deaths occurred in the LDCT screening group (196.6 cases per 1,000 participants) and 5,366 deaths in the CXR group (200.7 cases per 1,000 participants) (RR, 0.97 [95% CI, 0.94, 1.01]). The ITALUNG and LSS trials reported median pack per years instead of mean pack per years. The NELSON trial reported all-cause mortality for its primary analysis of the 13,195 males enrolled in the trial, excluding the 2,594 females that were enrolled. Therefore, the NELSON results in the figure above include only data for male participants (data were not reported for the female participants). The Nelson trial reported median age and median pack-years instead of mean age and mean pack-years.
Abbreviations: DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=Italian Lung Cancer Screening Trial; LSS=Lung Screening Study; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial.

Table 1. NSCLC Staging Overview, Typical 5-Year Survival, and Treatment Approaches[28, 257-261]

Stage	Description	TNM Classifications	5-Year Survival	Treatment Approach
I	Tumor ≤4 cm with no involvement of lymph nodes or distant metastasis	T1-2a N0 M0	77-92% for Stage 1a; 68% for Stage 1b	Surgical resection, including lobectomy; SBRT (mainly for nonsurgical candidates)
II	Tumor >4 cm and ≤7 cm with no involvement of lymph nodes or distant metastasis OR tumor ≤5 cm with metastases in ipsilateral pulmonary/hilar lymph nodes and no distant metastasis	T2b-3 N0 M0 T1-2 N1 M0	53-60%	Lobectomy + adjuvant chemotherapy
III	Heterogeneous group of disease, includes tumors ≥7 cm with or without ipsilateral lymph node involvement and smaller tumors with metastasis to the ipsilateral mediastinal/subcarinal nodes, contralateral mediastinal/hilar nodes, or supraclavicular nodes	T1-4 N0-3 M0	13-36%	Combined modality approach (chemotherapy, radiation therapy, +/- surgery, and/or immunotherapy)*
IV	Presence of distant metastasis: single or multiple extra-thoracic metastasis, malignant pleural or pericardial effusion	Any T or N M1a-c	1-10%	Combined modality approach (chemotherapy, radiation therapy, targeted molecular therapy and/or immunotherapy and +/- surgery)*

*Tailored to patient disease and performance status.

Abbreviations: a=separate tumor nodule[s] in contralateral lobe, tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusions; b=single extrapulmonary metastasis; c=multiple extrapulmonary metastases in one or more organs; M=distant metastasis; N=regional lymph nodes; NSCLC=non-small cell lung cancer; SBRT=stereotactic body radiation therapy; T=primary tumor; TNM=Tumor Node Metastasis.

Table 2. Characteristics of Included RCTs Evaluating Screening With LDCT Compared With CXR or With No Screening[a]

Study	Recruitment Years	Sample Size; Country	Mean Age (Ages Eligible)	% Male	Baseline Smoking Status	Eligibility Criteria for Pack-Years; Years Since Quitting	Screening Rounds, n	Screening Intervals, y	Total Median Followup, y	Quality
DANTE[61, 71, 72]	2001-2006	2,472; Italy	65 (60-74)	100	Current: 57% Former: 43% Mean pack-years: 47	≥20; <10 y	5	0, 1, 2, 3, 4	8.4	Fair
DLCST[65, 67]	2004-2006	4,104; Denmark	58 (50-70)	56	Current: 76% Former: 24% Mean pack-years: 36	≥20; quit after age 50 and <10 y ago	5	0, 1, 2, 3, 4	9.8	Fair
ITALUNG[62]	2004-2006	3,206; Italy	61 (55-69)	65	Current: 65% Former: 35% Median pack-years: 39	≥20 in the last 10 years or quit within the last 10 year	4	0, 1, 2, 3	9.3[†]	Fair
LSS[69, 70, 75]	2000-2001	3,318; U.S.	NR (55-74)	59	Current: 58% Former: 42% Median pack-years: 54	≥30; <10 y	2	0, 1	5.2	Fair
LUSI[59, 60, 73]	2007-2011	4,052; Germany	NR (50-69)	65	Current: 62% Former: 35% Mean pack-years: NR	≥25 y of 15 cigarettes[‡] or ≥30 y of 10 cigarettes[‡]; ≤10 y	5	0, 1, 2, 3, 4	8.8	Fair
NELSON[33, 76-79]	2003-2006	15,792; the Netherlands and Belgium	58 median (50-74)	84	Current: 55% Former: 45% Median pack-years: 38	>15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years; ≤10 y	4	0, 1, 3, 5.5	10	Fair
NLST[32, 56-58, 63, 64, 66, 68, 74]	2002-2004	53,542; U.S.	61 (55-74)	59	Current: 48% Former: 52% Mean pack-years: 56	≥30; ≤15 y	3	0, 1, 2	7 (and post-trial followup to 12.3 years)	Good

[*] NLST and LSS compared screening with LDCT vs. screening with CXR. All other trials compared screening with LDCT with no screening.

[†] The ITALUNG study reported 9.3 years for lung cancer–specific mortality and 8.5 years for lung cancer incidence.

[‡] The LSS was a feasibility pilot study.

Abbreviations: CXR=chest X-ray; DANTE=Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=Italian Lung Cancer Screening Trial; LDCT=low-dose computed tomography; LSS=Lung Screening Study; LUSI=The German Lung Cancer Screening Intervention Trial; n=number; NLST=National Lung Screening Trial; NR=not reported; RCT=randomized, controlled trial.

Table 3. Predictors Used in Risk Prediction Models for Identifying Adults at Higher Risk of Lung Cancer Mortality and Model Applicability

Model Name	LCDRAT[8] [4]	Kovalchik Model[56]	PLCOm2012[8] [5]	Simplified PLCOm2012[8] [3]	COPD-LUCSS[88]	Bach Model[90]	LLP Model[92]	Simplified LLP[83, 92*]	TSCE Incidence Model[93]	Knoke Model[96]	TSCE CPS Death Model[94]	TSCE NHS/HPFS Death Model[324]	HUNT Lung Cancer Model [95]
Risk Factors													
Personal													
Age	X	X	X	X	X[†]	X	X	X	X	X	X	X	X
Sex	X					X	X	X	X		X	X	
Race and/or ethnicity	X		X							X[‡]			
Body mass index	X	X	X		X[§]								X
Education (levels)	X[‖]		X[‖]										
Previous malignant tumor			X				X						
Smoking History													
Smoking status									X	X	X	X	
Cessation age										X			
Smoking duration	X		X	X		X	X[¶]	X[¶]	X	X	X	X	
Cigarettes per day	X		X	X		X			X	X	X	X	X
Pack-years	X[#]	X			X[#]								X
Quit duration	X	X[††]	X	X		X			X	X	X	X	X
Family History of Cancer													
Cases of lung cancer	X[‡‡]	X[‡‡]	X				X						
Age of onset of lung cancer							X[§§]						
Exposures and Lung Conditions													
Emphysema	X	X			X[‖‖]								
COPD			X										
Pneumonia							X						
Daily cough													X

Table 3. Predictors Used in Risk Prediction Models for Identifying Adults at Higher Risk of Lung Cancer Mortality and Model Applicability

Model Name	LCDRAT[8] [4]	Kovalchik Model[56]	PLCOm2012[8] [5]	Simplified PLCOm2012[8] [3]	COPD-LUCSS[88]	Bach Model[90]	LLP Model[92]	Simplified LLP[83, 92*]	TSCE Incidence Model[93]	Knoke Model[96]	TSCE CPS Death Model[94]	TSCE NHS/HPFS Death Model[324]	HUNT Lung Cancer Model [95]
Daily indoor exposure to smoke (hours)													X
Asbestos exposure						X	X						
Applying the Model Information													
Applicable to never smokers							X	X	X	X	X	X	
Applicable to former smokers	X	X	X	X	X	X	X	X	X	X	X	X	X
Applicable to current smokers	X	X	X	X	X	X	X	X	X	X	X	X	X
Model predicts risk of incidence	X		X	X	X	X	X	X	X				X
Model predicts survival	X[¶¶]	X								X	X	X	
Time horizon of prediction	5 y	5 y	6 y	6 y	NR	1 y (iterative)	5 y	5 y	1 y (iterative)	1 y (iterative)	1 y (iterative)	1 y (iterative)	6 and 16 years
Model formula printed			X	X	X	X	X	X	X	X	X	X	X
Discrimin-ation & calibration[##]													
Discrimination for lung cancer incidence (AUC) range	0.70-0.80	--	0.69-0.89	0.68-0.78	NR	0.68-0.78	0.66-0.79	0.66-0.74	0.67-0.78	0.67-0.77	0.62-0.74	0.67-0.78	0.87 (6 years)
Discrimination for lung cancer mortality (AUC) range	0.73-0.81	0.80	0.72-0.81	0.71-0.80	NR	0.71-0.80	0.67-0.77	0.68-0.79	0.68-0.79	0.68-0.78	0.63-0.77	0.68-0.79	NR
Calibration of model for lung cancer	0.94-1.06	--	0.87-0.98	1.02-1.04	NR	0.99-1.09	0.68-1.05	0.76-1.07	0.79-0.87	0.70-1.09	0.59-0.90	0.76-0.85	NR (shown as calibration plots that

Table 3. Predictors Used in Risk Prediction Models for Identifying Adults at Higher Risk of Lung Cancer Mortality and Model Applicability

Model Name	LCDRAT[8] [4]	Kovalchik Model[56]	PLCOm2012[8] [5]	Simplified PLCOm2012[8] [3]	COPD-LUCSS[88]	Bach Model[90]	LLP Model[92]	Simplified LLP[83, 92*]	TSCE Incidence Model[93]	Knoke Model[96]	TSCE CPS Death Model[94]	TSCE NHS/HPFS Death Model[324]	HUNT Lung Cancer Model [95]
incidence; range													show fairly good calibration)
Calibration of model for lung cancer mortality, range	0.94-1.31	0.97	0.95-1.01	1.02-1.19	NR	0.97-1.21	0.69-1.18	0.79-1.12	0.84-0.94	0.79-0.89	0.64-0.99	0.80-0.92	NR

* The simplified version of the LLP model uses the same parameter estimates as the original LLP model. However, when applying this model to a participant, it is assumed that only information on age and smoking history is known. Thus, the simplified model assumes that the participant had no prior diagnosis of pneumonia, no occupational exposure to asbestos, no prior diagnosis of a malignant tumor, and no family history of lung cancer.

† Age > 60

‡ Only applicable to white males ages 40 to 79 years.

§ BMI <25.

‖ 1≤12 grade; 2=high school graduate; 3=post-high school but not college; 4=some college; 5=bachelor's degree; 6=graduate school.

¶ Smoking duration levels for model: never; 1-20 years; 21-40 years; 41-60 years; >60 years.

Binary: >1 pack/day.

** Pack-years: >60.

†† Categories: 0=less than 1 year; 1=1 to 5 years; 2=more than 5 years.

‡‡ 0=No first-degree relatives with lung cancer; 1=1 first-degree relative with lung cancer; 2=2 or more first-degree relatives with lung cancer.

§§ Early onset (age <60 years); late onset (age ≥60 years).

‖‖ Radiologic emphysema.

¶¶ Model can estimate 10-year risk, but authors report 5-year estimates because the NLST only had 5.5 years of followup data.

LCDRAT: Cohorts used for external validation: PLCO-CXR and NLST-CXR. Discrimination higher in NHIS and PLCO vs. NLST cohorts. Calibration metric: Ratio of model-predicted cases to observed cases. A value of 1 indicates optimal calibration. **Kovalchik:** Cohort used for external validation: PLCO-CXR. Calibration metric: Ratio of model-predicted cases to observed cases.

PLCOm2012: Cohorts used for external validation: PLCO-CXR and control, 45 and UP study, NLST-CT and CXR, NHIS. Discrimination higher in PLCO vs. NLST cohorts. Calibration metric reported in table from ten Haaf et al: slope of calibration plot observed vs. expected. Perfect calibration if slope=1. Two studies reported calibration as the median (or mean) and 90th percentile absolute differences between observed and predicted risk probabilities, which ranged from 0.006-0.009 and 0.016-0.042, respectively.

For all other models except the HUNT model, discrimination and calibration are reported from the ten Haaf study. The range of discrimination and calibration outcomes are estimated using the NLST CT and CXR arms, and the PLCO-CXR and control arms. In general, discrimination and calibration were better in the PLCO cohorts than in the NLST cohorts. An exhaustive search and synthesis of risk model performance metrics was not in the scope of this review; thus, the numbers in this table are not a comprehensive description of discrimination and calibration reported in all studies of these models (inclusion was limited to studies that reported eligible benefits and harms outcomes and compared with USPSTF 2013 or NLST criteria).

Abbreviations: AUC=area under the curve; BMI=body mass index; COPD=chronic obstructive pulmonary disease; COPD-LUCSS=COPD-Lung Cancer Screening Score; CPS=Cancer Prevention Study; HPFS=Health Professionals Follow-Up Study; LCDRAT=Lung Cancer Death Risk Assessment Tool; LLP=Liverpool Lung Project; NHS=Nurses' Health Study; NLST=National Lung Screening Trial; PLCO=Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; TSCE=Two Stage Clonal Expansion Model.

Table 4. PLCOm2012 Model Estimated Benefits and Harms Over 6 Years Compared With USPSTF or NLST Criteria

Author, Year	Method for Determining Lung Cancer Incidence Risk Threshold	Risk Threshold	Cohort to Estimate Outcomes	Benefits	Harms: False-Positive Number (%)	Harms: False-Positive Rate
Tammemagi et al, 2013[85]	Fixed NLST population	1.35%	PLCO-CXR arm	Screen-prevented deaths: PLCOm2012: 81 NLST: 69 NNS: PLCOm2012: 174 NLST: 203	Model: 13,581 (96%) NLST: 13,662 (96.6%)	Model: 37.1 NLST: 37.3
Landy 2019 [89]	Fixed NLST population[32]	1.3%	NHIS 2015 data	Screen-prevented deaths: PLCOm2012: 56,528 USPSTF: 41,298 NNS: PLCOm2012: 222 USPSTF: 194	NR	NR
ten Haaf et al, 2017[83]	Fixed NLST population	1.35%	PLCO-CXR arm	NR	Model: 24904 (97.5%) NLST: 24784 (97.9%)	Model: 37.5 NLST: 37.8
ten Haaf et al, 2017[83]	Fixed NLST population	1.36%	PLCO-control arm	NR	Model: 24287 (97.7%) NLST: 24248 (97.8%)	Model: 38.3 NLST: 38.1
Weber et al, 2017[86]	Fixed NLST population	1.73%	45 and Up Study	NR	Model: 12,982 (96.9%) NLST: 12,929 (97.3%)	Model: 24.8 NLST: 24.7
Tammemagi et al, 2014[87]	NLST mortality benefit	1.51%	PLCO-CXR arm	NNS: Model: 225 USPSTF: NR	Model: 12378 (95.8%) USPSTF: 13688 (96.6%)	Model: 33.8 USPSTF: 37.3
Landy 2019 [89]	NLST mortality benefit[58]	1.51%	NHIS 2015 data	Screen-prevented deaths: PLCOm2012: 54,456 USPSTF: 41,298 NNS: PLCOm2012: 207 USPSTF: 194	NR	NR
Weber et al, 2017[86]	NLST mortality benefit	1.51%	45 and Up Study	NR	Model: 14,642 (97.1%) USPSTF: 13,800 (97.1%)	Model: 28.0 USPSTF: 23.7
Weber et al, 2017[86]	Optimal ROC classification	1.49%	45 and Up Study	NR	Model: 14,774 (97.1%) USPSTF: 13,800 (97.1%)	Model: 28.2 USPSTF: 23.7
Weber et al, 2017[86]	Conservative	2%	45 and Up Study	NR	Model: 11,168 (96.6%) USPSTF: 13,800 (97.1%)	Model: 21.3 USPSTF: 23.7
Landy 2019 [89]	Fixed USPSTF population	2.19%	NHIS 2015 data	Screen-prevented deaths: PLCOm2012: 47,401 USPSTF: 41,298 NNS: PLCOm2012: 169 USPSTF: 194	NR	NR

Abbreviations: CXR=chest X-ray; NLST=National Lung Screening Trial; NHIS=National Health Interview Survey; NNS=number needed to screen; NR=not reported; PLCO=Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; ROC=receiver operating characteristics; USPSTF=U.S. Preventive Services Task Force.

Table 5. Summary of Modeling Studies Evaluating Screen-Prevented Lung Cancer Deaths and NNS to Prevent One Lung Cancer Death*

Author, Year	Model	Comparator	Time Horizon, y	Risk Threshold (Selection Method)	Cohort to Estimate Outcomes (Sample Size)	Screen-Prevented Lung Cancer Deaths, Model vs. Comparator	NNS, Model vs. Comparator	FP per Prevented Deaths, Model vs. Comparator	Overdiagnosed Lung Cancers per Prevented Death, Model vs. Comparator
Tammemagi, 2013[85]	PLCOm2012 model	NLST	6	1.35% (fixed population)	PLCO-CXR arm (37,327)	81 vs. 69	174 vs. 203	167 vs. 196	1.04 vs. 1.04
Landy 2019[89]	PLCOm2012 model	USPSTF	6	1.3% (Reference Tammemagi et al 2013[32])	NHIS 2015 (12,600,000)	56,528 vs. 41,298	222 vs. 194	150 vs. 133	NR
Landy 2019[89]	PLCOm2012 model	USPSTF	6	1.51% (NLST mortality benefit-Reference Tammemagi et al 2014[58])	NHIS 2015 (11,300,000)	54,456 vs. 41,298	207 vs. 194	141 vs. 133	NR
Landy 2019[89]	PLCOm2012 model	USPSTF	6	2.19% (fixed population)	NHIS 2015 (8,000,000)	47,401 vs. 41,298	169 vs. 194	119 vs. 133	NR
Katki, 2016[84]	LCDRAT model	NLST	5	1.2% (fixed population)	NHIS 2010-2012 (9,018,130)	55,717 (95% CI, 53,033 to 58,400) vs. 46,488 (95% CI, 43,924 to 49,053)	162 (157-166) vs. 194 (187-201)	116 (113-119) vs. 133 (128-137)	0.91 vs. 0.93
Landy 2019[89]	LCDRAT model	USPSTF	5	1.2% (reference Katki, 2016[3])	NHIS 2015 (9,000,000)	53,732 vs. 41,298	168 vs. 194	119 vs. 133	NR
Landy 2019[89]	LCDRAT model	USPSTF	5	1.33% (fixed population)	NHIS 2015 (8,000,000)	51,019 vs. 41,298	156 vs. 194	112 vs. 133	NR
Katki, 2016[84]	LCDRAT model	NLST	5	0.9% (fixed effectiveness)	NHIS 2010-2012 (12,101,749)	62,382 (95% CI, 59,567 to 65,196) vs. 46,488 (95% CI, 43,924 to 49,053)	194 (188-200) vs. 194 (187-201)	134 (131-138) vs. 133 (128-137)	0.92 vs. 0.93
Kovalchik, 2013[56]	Kovalchik et al	NLST	5	0.84% (risk quintile 3-5)	NLST-CT (26,604)	77 vs. 88	208 vs. 302	78 vs. 108	NR
Kovalchik, 2013[56]	Kovalchik et al	NLST	5	1.23% (risk quintile 4-5)	NLST-CT (26,604)	64 vs. 88	166 vs. 302	64 vs. 108	NR

*Kovalchik et al applied a model to NLST, intrinsically conferring NLST benefits in lung cancer detection and mortality reduction. The other two studies assumed NLST-like benefits to calculated outcomes.

Abbreviations: CI=confidence interval; CXR=chest X-ray; FP=false positive; LCDRAT=Lung Cancer Death Risk Assessment Tool; NHIS=National Health Interview Survey; NLST=National Lung Screening Trial; NLST-CT=National Lung Screening Trial-Computerized Tomography arm; NNS=number needed to screen; NR=not reported; PLCO= Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; vs.=versus.

Table 6. Accuracy of LDCT for Lung Cancer Screening in RCTs (KQ 3)

Trial Name Author, Year	Number Analyzed	Nodule Classification Framework*	Threshold for Positive†	Screening Protocol	Sn	Sp	PPV	NPV
DANTE Infante, 2015[61]	2,450	I-ELCAP	>5-mm average diameter	5 annual screens	79.5%	75.5%	18.6%	98.1%
DLCST Pedersen, 2009[122]	4,104	DLCST	>15-mm maximum diameter or 5-15 mm with >25% volume increase on 3-month repeat	5 annual screens (4 reported)	NR	NR	9.5%	NR
ITALUNG Lopes Pegna, 2013[99]	1,406	I-ELCAP	≥5-mm average diameter solid nodule, ≥10-mm GGN average diameter, any part-solid nodule	4 annual screens‡	95.0%	26.4%	3.6%	99.4%
LSS Croswell, 2010[119]	1,610	NLST	≥3-mm maximum diameter T0, ≥4 mm maximum diameter for T1	2 annual screens	NR	NR	7.0%	NR
LUSI Becker, 2015[59]	2,028	I-ELCAP	≥5-mm average diameter	5 annual screens (4 completed)	93.5%	62%	7.2%	99.7%
MILD Sverzellati, 2016[82]	1,152	Modified NELSON	Volume >250 mm^3 or 60-250 mm^3 with >25% volume increase on 3-month repeat	5 annual screens	68.5%	99.2%	40.6%	99.7%
MILD Sverzellati, 2016[82]	1,151	Modified NELSON	Volume >250 mm^3 or 60-250 mm^3 with >25% volume increase on 3-month repeat	3 biennial screens	73.5%	99.2%	42.4%	99.8%
NELSON De Koning, 2020[76]	6,583§	NELSON	Volume >500 mm^3 or 50-500 mm^3 with VDT<400 d on 3-month repeat	4 rounds; baseline and after 1 y, 3 y, 5.5 y	59.0%	95.8%§	43.5%§	97.7%§
NLST Pinsky, 2013[101]	26,022	NLST	≥4-mm longest diameter	3 annual screens	93.1%	76.5%	3.3%	99.9%
UKLS Field, 2016[97]	1,994	Modified NELSON‖	Volume >500 mm^3 or 50-500 mm^3 with VDT<400 d on 3-month repeat	1 screen	NR	NR	36.8%	NR
Mean, range	NA	NA	NA	NA	80.3%, 59.0%-95.0%	76.4%, 26.4%-99.2%	21.3%, 3.3%-43.5%	99.2%, 97.7%-99.9%

* We categorized whether the approach to nodule classification was most similar to the approach used in NLST, NELSON, DLCST, or I-ELCAP.

† These are the abbreviated criteria for a positive screen. Studies also considered specific features of nodules, for example.

‡ Study ongoing at the time of this publication.

§ This evaluation excluded some NELSON participants because it was limited to males in the screening group (data were not presented for the 1,317 females in the screening group). The accuracy calculations in this row used NELSON's approach to classifying results, with indeterminate results that required a 3-month followup LDCT being categorized as negatives as long as the 3-month followup LDCT was negative (whereas other studies categorized the same type of thing, when any additional LDCT was required for evaluation, as a false positive).

‖ Nodules with volumes <50 mm^3 were split into two categories. Those <15 mm^3 received no further followup. Those 15-49 mm^3 received followup LDCT scan in 1 year.

Abbreviations: DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; GGN=ground-glass nodule; I-ELCAP=International Early Lung Cancer Action Program; ITALUNG=Italian Lung Cancer Screening Trial; LDCT=low-dose computed tomography; LSS=Lung Screening Study; LUSI=The German Lung Cancer Screening Intervention Trial; MILD=Multi-centric Italian Lung Detection; NA=not applicable; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial; NR=not reported; NPV=negative predictive value; PPV=positive predictive value; RCT=randomized, controlled trial; Sn=sensitivity; Sp=specificity; UKLS= UK Lung cancer Screening; VDT=volume doubling time.

Table 7. Accuracy of LDCT for Lung Cancer Screening in Nonrandomized Studies (KQ 3)

Author, Year	Trial/Database	Country	Number Analyzed	Threshold for Positive*	Screening Protocol	Sn	Sp	PPV	NPV
Crucitti, 2015[111]	"Un respiro per la vita"	Italy	1,500	>4 mm, avg max and min	1 scan	NR	34.0%	4.6%	NR
Henschke, 2004[131]	I-ELCAP	U.S.	2,698	≥5 mm, avg max and min	2 annual scans	97.0%	90.0%	Baseline: 20.9% Annual: 11.0%	Baseline: 99.2% Annual: 100%
Henschke, 2013[107]	I-ELCAP	Multinational	21,136	≥5 mm, avg max and min ≥6 mm, avg max and min	Annual scans; data is from baseline scans	NR† NR†	NR† NR†	3.5%† 5.5%†	NR† NR†
Toyoda, 2008[126]	Osaka	Japan	18,070	"Need for further clinical exam"	2 annual scans	88.9%	92.6%	NR	NR
Tsushima, 2008[123]	Azumi & Shinshu	Japan	2,486	>3 mm	Annual scans	100.0%	96.9%	9.9%	100.0%
Tammemagi, 2017[115]	PanCan	Canada	2,537	≥1 mm	T0: Baseline T1: 1 year T4: 4 years	92.7%	NR	NR	NR
Swensen, 2005[130]	Mayo	U.S.	1,520	NCN >4 mm, avg max and min	5 annual scans	95.5%	37.9%	5.8%	99.3%
Menezes, 2010[121]	Toronto	Canada	3,552	≥5 mm, avg max and min	6 annual screenings	87.7%	99.3%	NR	NR
Veronesi, 2008[127]	COSMOS	Italy	5,201	≥5 mm	1 scan	91.0%	99.7%	NR	NR
Mean, range	NA	NA	NA	NA	NA	93.3%, 87.7% to 100%	78.6%, 34.0% to 99.7%	8.7%, 3.5% to 20.9%	99.6%, 99.2% to 100%

* These are the abbreviated criteria for a positive screen. Studies also considered specific features of nodules, for example.

† Study reported data to allow calculation of PPV (reporting total positives and true positives) but did not report data to allow calculation of Sn, Sp, or NPV. However, an investigator from the study team submitted public comments on the draft report stating the following: Sn 97.5%, Sp 84.4%, and NPV 100% for the 5-mm threshold for a positive test and Sn 97.5%, Sp 90.3%, and NPV 100% for the 6-mm threshold for a positive test. The study also reported data for higher thresholds (7 mm, 8 mm, and 9 mm) that would allow calculation of PPV.

Abbreviations: avg=average; COSMOS=Continuing Observation of Smoking Subjects; I-ELCAP=International Early Lung Cancer Action Program; LDCT=low-dose computed tomography; max=maximum; min=minimum; NA=not applicable; NCN=National Cancer Network; NPV=negative predictive value; NR=not reported; PPV=positive predictive value; Sn=sensitivity; Sp=specificity; U.S.=United States.

Table 8. LDCT Parameters, by Study Type

	kV	mAs	Slice Width (mm)	Overlap*	Multi/Single Detector	Estimated Dose/Study (mSv)
Trials						
COSMOS[124, 134]	140	30	2.5	NR	MDCT	1.0 (men), 1.4 (women)
DANTE[71]	140	40	5	Yes	Both	NR
DLCST[122]	120	40	3 and 1, 1.5 and 1	Yes	MDCT	NR
ITALUNG[125]	120-140	20-43	3	NR	Both	NR
LSS[70]	120-140	60	5	NR	NR	NR
LUSI[60]	NR	NR	1	NR	MDCT	1.6-2
MILD[80]	120	30	0.75	NR	Both	0.7
NELSON[77]	80-140	40-80	0.7	Yes	MDCT	NR
NLST[32]	120-140	40-80	1-2.5	Yes	MDCT	1.5
Cohort Studies						
Crucitti et al, 2015[111]	120	35	1	No	MDCT	2.36
Mayo Lung Project[152]	120	40	3.75	NR	MDCT	0.65
PLuSS[137]	140	40-60	2.5	No	NR	NR
Toronto[118]	120	40-60	1-1.25	Yes	MDCT	NR
Tsushima et al, 2008[123]	120	25	5	NR	MDCT	NR

***** Overlap is an approach to image reconstruction. Helical (spiral) CT allows overlapping image reconstruction at arbitrary positions without additional radiation exposure to patients, theoretically increasing ability to detect smaller nodules (compared with consecutive reconstruction).

Abbreviations: COSMOS=Continuing Observation of Smoking Subjects; DANTE=Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=Italian Lung Cancer Screening Trial; LSS=Lung Screening Study; LUSI=The German Lung Cancer Screening Intervention Trial; MDCT=multidetector computed tomography; MILD=Multi-centric Italian Lung Detection; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial; NR=not reported; PLuSS=Pittsburgh Lung Screening Study.

Table 9. Number and Percentage of False-Positive Results After Screening With LDCT

Study Author, Year	Country	I-ELCAP or Lung-RADS	Screening Years	Definition of Positive Nodule by Study Authors*	False-Positive Results*	False-Positive Percentage*
Clinical Trials						
DLCST Pedersen, 2009[122] Saghir 2012[65]	Denmark	NA	Baseline	≥5 mm	T0: 162 T1: 34 T2: 39 T3: 32 T4: 35	T0: 7.90% T1: 1.7% T2: 2.0% T3: 1.6% T4: 1.9%
LSS Gohagan, 2004[70] Gohagan, 2005[69]	U.S.	NA	0, 1	Baseline: >3 mm Year 1: ≥4 mm	T0: 295 T1: 352	T0: 18.6% T1: 25.2%
LUSI Becker, 2015[59]	Germany	NA	0, 1, 2, 3, 4	≥5 mm Incidence nodules: VDT <600 of known nodule	T0: 428 T1: 77 T2: 65 T3: 95 T4: 82	T0: 21.1% T1: 4.1% T2: 3.5% T3: 5.2% T4: 5.2%
MILD Sverzellati, 2016[82]	Italy	NA	LDCT1 (annual screening): 0, T1, T2, T3, T4, T5, T6 LDCT2 (biennial screening): 0, T1, T2, T3 (T0.1, T1.1, and T2.1 indicate those converted to annual screening)	>60 mm^3 Incidence nodules: volume increase >25%	LDCT1: T0: 160 T1: 31 T2: 48 T3: 25 T4: 18 T5: 5 T6: 11 LDCT2 T0: 152 T0.1: 3 T1: 46 T1.1: 8 T2: 26 T2.1: 9 T3: 33 Total: 271	LDCT1: T0: 13.9% T1: 2.8% T2: 4.4% T3: 2.4% T4: 1.8% T5: 0.6% T6: 2.6% LDCT2 T0: 13.2% T0.1: 2.0% T1: 4.2% T1.1: 4.6% T2: 2.6% T2.1: 5.4% T3: 4.4% Total: 6.1%
NELSON van Klaveren, 2009[120] de Koning 2020[76]	Netherlands and Belgium	NA	0, 1, 3, 5.5	Volume >50 mm^3 (>9.8 mm in diameter) Incidence nodules: VDT <400 days	T0: 1,500† T1: 516† T2 (males only): 521 T3 (males only): 175	T0: 19.8%‡ T1: 7.1%‡ T2 (males only): 9.0% T3 (males only): 3.9%

Table 9. Number and Percentage of False-Positive Results After Screening With LDCT

Study Author, Year	Country	I-ELCAP or Lung-RADS	Screening Years	Definition of Positive Nodule by Study Authors*	False-Positive Results*	False-Positive Percentage*
NLST Aberle, 2011[32] Pinsky, 2014[64]	U.S.	NA	0, 1, 2	≥4 mm	T0: 6,921 T1: 6,733 T2: 3,843 <65 subgroup: T0: 4,796 T1: 4,678 T2: 2,603 ≥65 subgroup: T0: 2,125 T1: 2,058 T2: 1,232	T0: 26.3% T1: 27.2% T2: 15.9% <65 subgroup: T0: 24.8% T1: 25.7% T2: 14.6% ≥65 subgroup: T0: 30.3% T1: 31.5% T2: 19.5%
UKLS, Field, 2016[117]	U.K.	NA	Baseline	>50mm^3	494	26.90%
Cohort Studies						
NA Henschke, 2013[107]	International	I-ELCAP	Baseline	Based on size cut-off as indicated	5 mm: 3,277 6 mm: 2,040 7 mm: 1,385 8 mm: 965 9 mm: 727	5 mm: 15.5% 6 mm: 9.7% 7 mm: 6.6% 8 mm: 4.6% 9 mm: 3.4%
NLST LDCT cohort Yip, 2014[104]	U.S.	NA	Baseline	Based on size cutoff as indicated; assessed how false-positive screens would have been reduced if the NLST had used higher thresholds	5 mm: 3,848 6 mm: 2,470 7 mm: 1,621 8 mm: 1,144 9 mm: 858	5 mm: 14.4% 6 mm: 9.2% 7 mm: 6.1% 8 mm: 4.3% 9 mm: 3.2%

Table 9. Number and Percentage of False-Positive Results After Screening With LDCT

Study Author, Year	Country	I-ELCAP or Lung-RADS	Screening Years	Definition of Positive Nodule by Study Authors*	False-Positive Results*	False-Positive Percentage*
NLST LDCT cohort, if using Lung-RADS Pinsky, 2018[139]	U.S.	NA	Baseline, cumulative (includes up to 2 annual screens)	Lung-RADS	NR	Risk decile (based on Tammemagi risk prediction model, 6-year lung cancer risk): Baseline 1: 8.3% 2: 9.8% 3: 11.0% 4: 10.1% 5: 11.6% 6: 11.9% 7: 13.1% 8: 13.8% 9: 14.7% 10:17.6% Cumulative 1: 12.9% 2: 15.3% 3: 16.2% 4: 15.7% 5: 18.3% 6: 19.2% 7: 21.3% 8: 20.7% 9: 22.3% 10: 25.9%

Table 9. Number and Percentage of False-Positive Results After Screening With LDCT

Study Author, Year	Country	I-ELCAP or Lung-RADS	Screening Years	Definition of Positive Nodule by Study Authors*	False-Positive Results*	False-Positive Percentage*
VHA demonstration Kinsinger, 2017[38]	U.S.	NA	Baseline	Not reported clearly in the paper but cited Fleischner guidelines from 2013 state any nodule ≥5 mm; also recommended followup of small nodules if they were new, were growing, or had suspicious features.	All sites: 1,226 Site 1: 333 Site 2: 66 Site 3: 178 Site 4: 238 Site 5: 153 Site 6: 61 Site 7: 109 Site 8: 88	All sites: 58% of veterans screened; 28.9% of those eligible for screening Percentages below are of those eligible for screening: Site 1: 38.3% Site 2: 14.0% Site 3: 45.8% Site 4: 30.6% Site 5: 53.1% Site 6: 22.4% Site 7: 12.6% Site 8: 28.0%
NA Menezes, 2010[121]	Canada	I-ELCAP	0, 1, 2, 3, 4, 5	≥5 mm	Baseline: 556 Y1: 249 Y2: 64 Y3: 9 Y4: 5 Y5: 2	Baseline: 16.6% Y1: 9.3% Y2: 9.6% Y3: 5.2% Y4: 13.9% Y5: 28.6%
NA Henschke, 2006[128]	Japan	I-ELCAP	0, 1	≥5 mm Incidence nodules: any new nodule	Baseline: 3,781 Annual: 1,386	Baseline:12% Annual: 5.0%
NA Henschke, 2004[131]	U.S.	I-ELCAP	0, 1	≥5 mm Incidence nodules : any new nodule	I-ELCAP 1: Baseline: 130 Annual: 137 I-ELCAP 2: Baseline: 238 Annual: 117	I-ELCAP 1: Baseline: 9.6% Annual: 12.2% I-ELCAP 2: Baseline: 9.9% Annual: 5.2%
NA Swensen, 2005[130]	U.S.	NA	0, 1, 2, 3, 4	>4 mm (initially followup for any nodule was at least 6 months but later moved out to 12 months)	Baseline: All nodules: 749 >4 mm: 404 Incidence: All nodules: 773 >4 mm: 378	Baseline: All nodules: 49.3% >4 mm: 26.6% Incidence: All nodules: could not calculate >4 mm: could not calculate

Table 9. Number and Percentage of False-Positive Results After Screening With LDCT

Study Author, Year	Country	I-ELCAP or Lung-RADS	Screening Years	Definition of Positive Nodule by Study Authors*	False-Positive Results*	False-Positive Percentage*
NA Tsushima, 2008[123]	Japan	NA	Baseline	<3 mm solid	175	7.0%
PLuSS Wilson, 2008[137]	U.S.	NA	0,1	0.5-0.9 cm average diameter with spiculated border or > 1.0 cm average diameter.	741	20.30%
NA Crucitti, 2015[111]	Italy	NA	0, 1	Noncalcified nodule of any size resulted in another CT after 1 year; NCN ≥5 mm indicated further evaluation	Baseline: 500	Baseline: 33.3%

* Definition of positive for these calculations was the threshold leading to further evaluation (further CT scans, biopsy, etc.), including CT scans at intervals shorter than the next routine screening CT scan. False-positive results calculated using the number of tests leading to further evaluation (further CT scans, biopsy, etc.) and false-positive percentage calculated by dividing the number of false-positive results by the number of people screened with LDCT scan.

† Data reported here based on the systematic review's definition of positive tests. If indeterminant results are reclassified based on 3-month followup LDCT scans, then the number of false-positive results for the first two screening rounds would be 196 and 128, respectively. The protocol for reading nodules included the freedom of radiologists to manually up- or downgrade results. This led to a net decrease of 119 false-positive results in the baseline round.[325]

‡ Data reported here based on the systematic review's definition of positive tests. If indeterminant results are reclassified based on 3-month followup LDCT scans, then the false-positive percentage (percentage of all persons screened) would be 1.7 percent and 1.0 percent, respectively.

Abbreviations: DLCST=Danish Lung Cancer Screening Trial; I-ELCAP=International Early Lung Cancer Action Program; LDCT=low-dose computed tomography; LUSI=German Lung Cancer Screening Intervention Trial; MILD=Multi-centric Italian Lung Detection; NA=not applicable; NCN=National Cancer Network; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial; NLST-CT=National Lung Screening Trial-Computed Tomography; PLuSS=Pittsburgh Lung Screening Study; T=time; U.K.=United Kingdom; UKLS= UK Lung cancer Screening; U.S.=United States; VHA=Veterans Health Administration; VDT=volume doubling time.

Table 10. False-Positive Evaluations

Author, Year Country	Associated Trial Nodule Management (I-ELCAP or Lung-RADS) N Participants Screened with LDCT	Needle Biopsies and Complications Following a False Positive Result Among Participants Screened with LDCT N (%)	Other Procedures and Complications Following a False Positive Result Among Participants Screened with LDCT N (%)	Surgical Procedures and Complications Following a False Positive Result Among Participants Screened with LDCT N (%)
Aberle, 2011[32] U.S.	NLST NA 26,722	66 (0.25) Most severe complication classified as major:* 0 (0) Most severe complication classified as intermediate:† 6 (0.02) Most severe complication classified as minor:‡ 1 (0.004) Death within 60 days: 0 (0)	Bronchoscopy: 227 (0.85) Most severe complication classified as major:* 2 (0.007) Most severe complication classified as intermediate:† 9 (0.034) Most severe complication classified as minor:‡ 0 (0) Death within 60 days: 4 (0.015)	Thoracotomy, thoracoscopy, or mediastinoscopy: 164 (0.61) Most severe complication classified as major:* 9 (0.034) Most severe complication classified as intermediate:† 13 (0.049) Most severe complication classified as minor:‡ 4 (0.015) Death within 60 days: 2 (0.007)
Becker, 2012[60] Germany	LUSI NA 2,029	9 (0.44)	NR	NR
Church, 2013[57] U.S.	NLST NA 26,715	Bronchoscopy, with biopsy: 108 (0.40)	Bronchoscopy, without biopsy: 42 (0.16) Other procedure: 122 (0.46)	Mediastinoscopy or mediastinotomy: 12 (0.045) Thoracoscopy: 38 (0.14) Thoracotomy: 41 (0.15)
Croswell, 2010[119] U.S.	NA NA 1,610	NR	Bronchoscopy (minimally invasive): 25 (1.55) Lung biopsy, mediastinoscopy, mediastinotomy, thoracentesis, or VATS thoracoscopy (moderately invasive): 20 (1.24)	Lung resection and thoracotomy (major surgical procedure): 8 (0.50)
Field, 2016[117] U.K.	UKLS Trial NA 1,994	7 (0.35)	EBUS: 1 (0.05)	NR
Infante, 2011[140] Italy	DANTE NA 1,276	NR	NR	Total surgical procedure: 17 (1.33) Mediastinoscopy: 3 (0.24) VATS wedge resection: 7 (0.55) Open wedge resection: 6 (0.47) Open segmentectomy:1 (0.08)

Table 10. False-Positive Evaluations

Author, Year Country	Associated Trial Nodule Management (I-ELCAP or Lung-RADS) N Participants Screened with LDCT	Needle Biopsies and Complications Following a False Positive Result Among Participants Screened with LDCT N (%)	Other Procedures and Complications Following a False Positive Result Among Participants Screened with LDCT N (%)	Surgical Procedures and Complications Following a False Positive Result Among Participants Screened with LDCT N (%)
Lopes Pegna, 2013[99] Italy	ITALUNG I-ELCAP 1,406	1 (0.07)	NR	Surgical resection: 4 (0.28)
Menezes, 2010[121] Canada	NA I-ELCAP 3,352	3 (0.09)[§] Pneumothorax: 1 (0.03)	NR	NR
Pinsky, 2014[64] U.S.	NLST NA **Under 65 Cohort** Year 0: 19,306 Year 1: 18,184 Year 2: 17,798 Total: 55,288 LDCTs **65+ Cohort** Year 0: 7,003 Year 1: 6,531 Year 2: 6,304 Total: 19,838 LDCTs	NR Total complications: Year 0: 18 (0.07) Year 1: 16 (0.06) Year 2: 13 (0.05) Note: these were reported as complications for invasive procedures and NR how many were attributable to biopsies.	Invasive Procedures / Total Complications / Major Complications **Under 65** Year 0: 168 (0.87) / 10 (0.05) / 1 (0.01) Year 1: 84 (0.46) / 14 (0.08) / 2 (0.01) Year 2: 73 (0.41) / 8 (0.04) / 3 (0.02) Total: 325 (0.59) / 32 (0.06) / 6 (0.01) **65+** Year 0: 86 (1.23) / 8 (0.11) / 2 (0.03) Year 1: 44 (0.67) / 2 (0.03) / 2 (0.03) Year 2: 47 (0.75) / 5 (0.08) / 2 (0.03) Total: 177 (0.89) / 15 (0.08) / 6 (0.03) Of all LDCTs, invasive procedures after false-positive screens: 3.3% vs. 2.7% for those ≥65 vs. <65 (p=0.039).	**Under 65** Baseline: 60 (0.31) Year 1: 34 (0.19) Year 2: 25 (0.14) Total: 119 (0.22) **65+** Baseline: 29 (0.41) Year 1: 17 (0.26) Year 2: 18 (0.29) Total: 64 (0.32)
Swensen, 2005[130] U.S.	NA NA 1,520	NR	NR	13 (0.86) participants underwent 15 surgeries Surgical mortality: 0 (0)

Table 10. False-Positive Evaluations

Author, Year Country	Associated Trial Nodule Management (I-ELCAP or Lung-RADS) N Participants Screened with LDCT	Needle Biopsies and Complications Following a False Positive Result Among Participants Screened with LDCT N (%)	Other Procedures and Complications Following a False Positive Result Among Participants Screened with LDCT N (%)	Surgical Procedures and Complications Following a False Positive Result Among Participants Screened with LDCT N (%)
van 't Westeinde, 2012[138] Netherlands/Belgium	NELSON NA 7915	NR	Bronchoscopy: 121 (1.53)	NR
Veronesi, 2008[127] Italy	NA NA 5,201	NR	NR	Surgical biopsy: 15 (0.29)
Veronesi, 2012[135] Italy	COSMOS NA 5,203	29 (0.56)	NR	NR
Wagnetz, 2012[118] Canada	NA I-ELCAP 4,782	20 (0.42)	NR	VATS: 5 (0.10)
Walker, 2015[133] U.S.	NA Lung-RADS 1,654	NR	NR	5 (0.30) Surgery-related deaths: 0 (0)

* Major complications: Acute respiratory failure, anaphylaxis, bronchopulmonary fistula, stroke, cardiac arrest, cardiac vascular accident, congestive heart failure, tube placement, death, hemothorax, myocardial infarction, respiratory arrest, tube thoracostomy or other drainage for more than 4 days, wound dehiscence; bronchial stump leak, empyema, injury to vital organ or vessel, mechanical ventilation over 48 hours post-op, complications requiring intervention, thromboembolic complication, chylous fistula, brachial plexopathy, lung collapse, infarcted sigmoid colon.

† Intermediate complications: Blood loss requiring a transfusion, cardiac arrhythmia requiring medical attention, fever requiring antibiotics, hospitalization post procedure, referral to a pain specialist, pneumothorax requiring tube placement, rib fracture(s), vocal cord immobility/paralysis, requiring antibiotics, ST elevation, infections, cardiac ischemia, bronchitis, pneumonia, pleural effusion, sepsis, respiratory distress, mucous plug requiring bronchoscopy, steroid-induced diabetes.

ǂ Minor complications: Allergic reaction, bronchospasm, vasovagal reaction/hypotension, subcutaneous emphysema, atelectasis, pneumothorax with no chest tube, ileus, seroma, paresthesias/hyperesthesias.

Table 10. False-Positive Evaluations

[§] Four additional individuals who were not diagnosed with lung cancer (although followup was ongoing at the time of publication) were recommended to have biopsies. Of those four, two people had insufficient biopsies limited by low cellularity, one had a pneumothorax prior to a sample being obtained, and one had resolution of the nodule prior to a biopsy being obtained.

Abbreviations: COSMOS=Continuing Observation of Smoking Subjects; DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays; EBUS=endobronchial ultrasound; I-ELCAP=International Early Lung Cancer Action Program; ITALUNG=Italian Lung Cancer Screening Trial; LUSI=German Lung Cancer Screening Intervention Trial; N=number of participants; NA=not applicable; NLST=National Lung Screening Trial; NR=not reported; U.K.=United Kingdom; UKLS=UK Lung cancer Screening; U.S.=United States; VATS=video-assisted thoracoscopic surgery; Y=year.

Table 11. Summary of Evidence on Screening for Lung Cancer With LDCT

Table Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 1. Benefits of screening	k=7 RCTs (26 publications), 86,486 participants	The good-quality NLST (n=53,542) reported a reduction in lung cancer mortality (IRR 0.85 [95% CI, 0.75 to 0.96]) and all-cause mortality (IRR 0.93 [95% CI, 0.88 to 0.99]) with three rounds of annual LDCT compared with CXR (NNS=323 to prevent 1 lung cancer death over 6.5 years). NELSON (n=15,792) found a reduction in lung cancer mortality (IRR, 0.75 [95% CI, 0.61 to 0.90]) but not all-cause mortality (IRR, 1.01 [95% CI, 0.92 to 1.11]) with four rounds of LDCT screening using volumetric measurements with increasing intervals (baseline, 1 year, 3 years, and 5.5 years) compared with no screening (NNS=130 to prevent 1 lung cancer death over 10 years).	Consistent among trials adequately powered; precise	Good: 1 Fair: 6	All but two of the seven trials were underpowered to assess for a lung cancer mortality benefit.	High for benefit*	High-risk current and former smokers (with ≥30 pack-years [NLST] or >15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years [NELSON]); ages 50-74; NLST and NELSON participants were younger, more highly educated, and less likely to be current smokers than the U.S. screening-eligible population; limited racial and ethnic diversity; US population eligible for screening faces higher risk of death from competing causes than trial participants; mainly conducted at large academic centers; NLST did not use current U.S. screening protocols such as Lung-RADS; NELSON used volumetric measurements for screening.

Table 11. Summary of Evidence on Screening for Lung Cancer With LDCT

Table Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 2. Risk prediction models	k=9; 13 risk prediction models evaluated in 9 cohorts comprising 21,922,733 participants	**Benefits:** Studies of three models (PCLOm2012, LCDRAT, and Kovalchik model) reported increased screen-preventable deaths compared with risk factor–based criteria (k=4; 21,682,066 participants from 4 cohorts). Most findings from these studies also showed improved NNS. **Harms:** Most studies did not report on actual harms of screening. Studies of all models reported similar numbers of false-positive selections for screening (i.e., the model selected people to be screened who did not have or develop lung cancer or death from lung cancer) and mixed findings for rates of false-positive selections or false-positive selections per prevented death when comparing risk prediction models to risk factor–based criteria.†	Consistent; imprecise (results highly dependent on risk threshold selected)	Good: 6 Fair: 3	No trials have compared use of a risk prediction model with risk factor-based criteria; evidence base is limited by lack of an established risk threshold; most models were evaluated by a single study in one to two cohorts.	Low for greater benefits and similar or reduced harms	High-risk current and former smokers; mainly applicable to NLST or USPSTF screen-eligible persons (ages 55-74 years or 55-80 years)
KQ 3. Accuracy of screening with LDCT	k=24 n=107,200	Sensitivity ranged from 59% to 100% (k=13, n=76,856) and was over 80% in vast majority of studies. Specificity ranged from 26.4% to 99.7% (k=13, n=75,819) and was over 75% in vast majority. PPV ranged from 3.3% to 43.5%. NPV ranged from 97.7% to 100%. Reliability among radiologists was fair to moderate (k=3).	Reasonably consistent; imprecise (except precise for NPV)	Good: 3 Fair: 21	Incomplete or unreported followup length may have led to differential measurement. Heterogeneity in screening protocols and definitions (e.g., positive tests, indeterminate tests).	Moderate	U.S. and highly developed countries; most conducted in past 10 years. Similar LDCT technologies used across studies; varying nodule classification protocols that could likely be replicated in the U.S.; few studies used nodule classification approach recommended by ACR (Lung-RADS).

Table 11. Summary of Evidence on Screening for Lung Cancer With LDCT

Table Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQs 4 and 5. Harms of screening, workup, or surveillance	Radiation: k=9 n=74,963 participants	**Radiation from 1 LDCT**: range 0.65 mSv to 2.3 6mSv **Cumulative radiation exposure:** 20.8 mSv to 32.5 mSv for annual screening for 25 years **Radiation-induced cancer:** 0.26 to 0.81 major cancers for every 1,000 people screened with 10 annual LDCTs[‡]	Consistent; imprecise	Good: 3 Fair: 6	Estimates of radiation-induced cancers are based on modeling.	Moderate for radiation-induced harms	Estimates were not provided for lifetime risk of radiation-induced cancers or fatal cancers from annual screening from 55 to 80 (i.e., USPSTF 2013 recommendation).
	False positives: k=27 n=115,6544 participants False-positive followup evaluations: k=14 n=56,223 participants	**False-positive rates:** range 7.9%-49.3% for baseline screening and 0.6%-28.6% for incidence screening rounds; rates generally declined with each round. NLST reported 26.3%, 27.2%, and 15.9% for baseline, year 1, and year 2, respectively; rates were lower in NELSON; the VA implementation study reported 58% of those screened (28.9% of screen-eligibles) at baseline and over 30% variation across eight sites. **Invasive procedures for false-positive results,** range of rates for every 1,000 people screened (NLST rate): 0.9 to 5.6 needle biopsies (2.5) resulting in 0.3 to 0.7 complications; 5 to 13 surgical procedures; (17 total invasive procedures, resulting in <1 major complication[§])	Consistent; imprecise	Good: 8 Fair: 19 Good: 4 Fair: 10	Heterogeneity in screening protocols, definitions of positive and false-positive results, and reporting of procedures and complication rates.	Moderate for harms due to false-positive results	Most studies did not use current nodule evaluation protocols such as Lung-RADS; an evaluation using NLST data estimated that 23.4% of all invasive procedures for false-positive results from the NLST would have been prevented by using Lung-RADS.
	Overdiagnosis: k=12 n=95,290 participants	**Overdiagnosis**: Estimates ranged from 0% to 67.2% that a screen-detected lung cancer is overdiagnosed; NLST data indicate approximately 4 cases of overdiagnosis over 6.5 years (and 3 lung cancer deaths prevented) per 1,000 people screened.[‖]	Inconsistent; imprecise	Good: 2 Fair: 10	Inadequate duration of followup and heterogeneity limit the evaluation.	Low for harms	NLST estimate is based on 3 annual screens and 6.5 years of followup; uncertain whether it would increase or decrease with ongoing screening and longer followup.

Table 11. Summary of Evidence on Screening for Lung Cancer With LDCT

Table Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
	Smoking behavior: k=7 n=29,038 participants	**LDCT vs. no screening (k=2):** Evidence on cessation an intensity does not indicate harm of false reassurance. **Positive or indeterminate results vs. normal results:** Abnormal or indeterminate results may increase cessation and continued abstinence, but normal screening test results had no influence.	Inconsistent; Imprecise	Good: 0 Fair: 7	Most RCTs of LDCT did not report on outcomes to assess for false reassurance.	Low for no harms	The two RCTs providing data for LDCT vs. no screening were conducted in Denmark (DLCST) and the Netherlands and Belgium (NELSON).
	Psychosocial harms: k=9 n=14,715 participants	**General HRQoL:** No significant differences over 6 months to 2 y of followup between LDCT and controls (k=2 RCTs, n=3,937); worse HRQoL for persons receiving true-positive results vs. other results. **Anxiety and depression:** No significant increase over 2 weeks to 2 y of followup for LDCT vs. controls (k=6 RCTs, n=12,096); increased anxiety for individuals receiving true-positive results vs. other results. **Distress:** no significant increase over approximately 2 y of followup for LDCT vs. controls (k=2 RCTs, n=5,180); temporary increase for those receiving indeterminate results vs. other results. **Other potential psychosocial consequences of screening:** each generally assessed by a single study, often without a non-LDCT comparison group, and not indicative of harm	Reasonably consistent and precise for HRQoL, anxiety and depression, and distress Consistency unknown and imprecise for other outcomes	Good: 1 Fair: 8	Relatively short followup (2 y or less); RCTs did not assess these outcomes over the duration of the trials.	Moderate for no harm over 2 y (HRQoL, anxiety, and distress) for LDCT vs. controls. Moderate for worse short-term HRQoL, anxiety, and distress for those who received true-positive or indeterminate results vs. other results	High-risk current and former smokers; studies lacked racial and ethnic diversity; most studies conducted in Europe; trials did not use current protocols such as Lung-RADS.

Table 11. Summary of Evidence on Screening for Lung Cancer With LDCT

Table Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
	Incidental findings (IFs): k=7 n=80,485	Rates of reported significant IFs ranged from 4.4 to 40.7%. Common IFs were coronary artery calcification; aortic aneurysms; emphysema; infectious and inflammatory processes; and masses, nodules, or cysts of the kidney, breast, adrenal, liver, thyroid, pancreas, spine, and lymph nodes. IFs led to consultations, additional imaging, and invasive procedures. Nonlung cancers were diagnosed in 0.39% of NLST LDCT arm participants during screening. **Incidental detection of thyroid cancer:** In NLST,¶ thyroid cancer incidence was roughly double during 3 years of active LDCT screening compared with CXR screening (HR, 2.19 [95% CI, 1.07–4.47]), but not during subsequent years (HR,1.08 [95% CI, 0.49–2.37]).	Consistent; imprecise	Fair: 7	No standard definition for which IFs were significant or actionable. Few studies on followup evaluations and distal outcomes.	Moderate for harms	Screen-eligible adults undergoing LDCT in academic or tertiary lung cancer screening centers.

Table 11. Summary of Evidence on Screening for Lung Cancer With LDCT

Table Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 6. Efficacy of surgical resection for Stage I NSCLC	k=36 uncontrolled cohort studies n=212,274	**5-year OS for surgical resection** (including lobectomy and SLR approaches), range: 33 to 86% for Stage I, 58 to 83% for Stage IA, and 42 to 79% for Stage IB. In pathologic Stage I patients in the NCDB from 2003 to 2006 the 5-year OS was 61% for surgical resection (n=54,350). Survival rates in the NCDB, SEER, and VA VINCI databases for Stage I, covering the years 2003-2015, ranged from 53% to 75% for lobectomy (n=23,707). Survival rates were generally higher for lobectomy than SLR, for smaller than larger tumors, and for patients who are female, younger, nonsmokers, or had fewer comorbidities than patients who are male, older, smokers, or sicker.	Reasonably consistent; imprecise	Good: 5 Fair: 31	Information related to deviations from intervention, missing data, and sources of survival outcomes often lacking; heterogeneity related to staging of NSCLC (clinical or pathologic) and surgical approaches (among studies and over time).	Moderate for benefit	Persons with Stage I NSCLC; some studies were more than 10 years old and may be less applicable to current approaches and outcomes (studies were from 1983 to 2018)
KQ 6. Efficacy of SBRT for Stage I NSCLC	k=27 uncontrolled cohort studies n=38,915	5-year OS (and other measures of long-term survival) varied substantially across studies (range: 20 to 80%) and by subgroups defined by clinical characteristics (e.g., operability of tumor) and patient age; survival may be higher among younger than older patients.	Inconsistent; imprecise	Good: 2 Fair: 25	Information related to deviations from intervention, missing data, and sources of survival outcomes often lacking; substantial heterogeneity related to staging and operability of tumors.	Low for benefit	Persons with operable or inoperable Stage I NSCLC

Table 11. Summary of Evidence on Screening for Lung Cancer With LDCT

Table Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 7. Harms of surgical resection	k=29 uncontrolled cohort studies n=755,427	30-day mortality rates ranged from 0 to 4% in most studies; rates of 90-day mortality were slightly higher (range: 2 to 5% in most studies). Less than one-third of patients in most studies experienced treatment-related adverse events. Adverse events reported in ≥10% of patients included pulmonary events (e.g., air leak, pleural effusion) and cardiac arrhythmias.	Reasonably consistent; reasonably precise	Good: 3 Fair: 26	Information related to deviations from intervention, missing data, and sources of survival outcomes often lacking; potential selective reporting of adverse events.	Moderate for harms	Persons having lobectomy or SLR for the treatment of Stage I NSCLC
KQ 7. Harms of stereotactic body radiation therapy	k=1 RCT (comparing dosing regimens), 1 uncontrolled clinical trial, and 58 uncontrolled cohort studies n=49,654	30- and 90-day mortality rates ranged from 0 to 3%. Adverse events were experienced by a majority of patients, but most were of mild or moderate severity. Adverse events reported in ≥10% of patients included were pulmonary events (e.g., cough, dyspnea, pneumonitis, fibrosis) or respiratory disorders (including dyspnea), chest wall pain, fatigue, and dermatologic reactions. Incidence of rib fracture ranged from 0% (n=80 patients) to 42% (n=169 patients).	Reasonably consistent; imprecise	Good: 1 Fair: 59	Information related to deviations from intervention, missing data, and sources of survival outcomes often lacking; potential selective reporting of adverse events.	Low for harms	Persons having SBRT/SABR for the treatment of operable or inoperable Stage I NSCLC
KQ 8. Change in mortality from a specified change in lung cancer incidence (and stage shift)	k=2 RCTs (NLST and NELSON) n=69,334	An absolute increase in lung cancer incidence of 0.5-0.6%, increase in Stage I lung cancers of 19-27%, decrease in Stage IV lung cancers of 14-19% were associated with 52-83 fewer lung cancer deaths and 0 (NELSON) to 84 (NLST) fewer all-cause deaths per 100,000 person-years.	Consistent; precise for lung cancer mortality but imprecise for all-cause mortality	Good: 1 Fair: 1	Reporting bias not detected.	High	3 annual rounds of screening with LDCT (compared with CXR) in NLST or 4 rounds of screening with increasing intervals as conducted in NELSON (volumetric approach); applicable to workup of lung cancers and subsequent treatments used in the NLST and NELSON; same applicability issues as listed for KQ 1.

* Strength of evidence was graded as moderate prior to final publication of NELSON because of unknown consistency (with a single good quality study that was adequately powered) but was changed to high after including NELSON in the evidence report.

Table 11. Summary of Evidence on Screening for Lung Cancer With LDCT

† The language "false positive" here refers to model performance metrics with respect to lung cancer events (diagnosis or deaths), not with respect to LDCT results.
‡ One study estimated a lifetime risk of fatal cancer of 0.11 per 1,000 subjects after the four screening rounds.[136]
§ NLST reported 11 major complications and 6 deaths within 60 days of invasive procedures among those with false-positive results (2 deaths after surgical resections and 4 after bronchoscopy).
‖ Based on converting data to per 1,000 screened from study that reported 1.38 cases of overdiagnosis in every 320 patients needed to screen to prevent one death from lung cancer.[142]
¶ This study specifically addressed the potential for overdiagnosis of thyroid cancer through incidental detection.
Abbreviations: ACR=American College of Radiology; CI=confidence interval; CPS=Cancer Prevention Study; CXR=chest X-ray; DLCST=Danish Lung Cancer Screening Trial; HR=hazard ratio; HRQoL=hazard ratio quality of life; IFs=incidental findings; IRR=incidence rate ratio; KQ=key question; LCDRAT=Lung Cancer Death Risk Assessment Tool; LCRAT=Lung Cancer Risk Assessment Tool; LDCT=low-dose computed tomography; LLP=Liverpool Lung Project; n=number; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NHS=Nurses' Health Study; NLST=National Lung Screening Trial; NNS=number needed to screen; NPV=negative predictive value; NSCLC=non-small cell lung cancer; OS=overall survival; PPV=positive predictive value; RCT=randomized, controlled trial; SABR=stereotactic ablative radiation; SBRT=stereotactic body radiotherapy; SLR=sublobar resection; TSCE=Two-Stage Clonal Expansion; USPSTF=U.S. Preventive Services Task Force; VA=Veteran's Administration.

Appendix A Table 1. Overview of Lung-RADS Classification System (Version 1.0)

Category Classification	Category Descriptor	Category	Findings	Management
Incomplete		0	Part or all of lungs cannot be evaluated Prior chest CT examination(s) being located for comparison	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed
Negative	No nodules and definitely benign nodules	1	No lung nodules Nodule(s) with specific calcifications: complete, central, popcorn, concentric rings, and fat- containing nodules	Continue annual screening with LDCT in 12 months
Benign appearance or behavior	Nodules with a very low 90% likelihood of becoming a clinically active cancer due to size or lack of growth	2	Solid nodule(s): <6 mm, new <4 mm Part solid nodule(s): <6 mm total diameter on baseline screening Nonsolid nodule(s) (GGN): <20 mm OR ≥20 mm and unchanged or slowly growing Category 3 or 4 nodules unchanged for ≥3 months	Continue annual screening with LDCT in 12 months
Probably benign	Probably benign finding(s): short-term followup suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	Solid nodule(s): ≥6 to <8 mm at baseline OR new 4 mm to <6 mm Part solid nodule(s) ≥6 mm total diameter with solid component <6 mm OR new <6 mm total diameter nonsolid nodule(s) (GGN) ≥20 mm Nonsolid nodule(s) (GGN) ≥20 mm on baseline CT or new	6-month LDCT
Suspicious	Findings for which additional diagnostic testing and/or tissue sampling is recommended	4A	Solid nodule(s): ≥8 to <15 mm at baseline OR growing <8 mm OR new 6 to <8 mm Part solid nodule(s): ≥6 mm with solid component ≥6 mm to <8 mm OR with a new or growing <4 mm solid component Endobronchial nodule	3-month LDCT; PET/CT may be used when there is a ≥8 mm solid component
		4B	Solid nodule(s) ≥15 mm OR new or growing and ≥8 mm Part solid nodule(s) with a solid component ≥8 mm OR a new or growing ≥4 mm solid component	Chest CT with or without contrast, PET/CT and/or tissue sampling depending on the *probability of malignancy and comorbidities. PET/CT may be used when there is a ≥8 mm solid component.
		4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy	

Adapted from Lung-RADS™ Version 1.0 Assessment Categories Release date: April 28, 2014
Abbreviations: CT=computed tomography; GGN=ground glass nodule; LDCT=low-dose computed tomography; PET=positron emission tomography.

Appendix A Table 5. Recommendations for Lung Cancer Screening With LDCT

Category Classification	Category Descriptor	Category	Findings	Management
Incomplete		0	Part or all of lungs cannot be evaluated; prior chest CT examination(s) being located for comparison	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed
Negative	No nodules and definitely benign nodules	1	No lung nodules; nodule(s) with specific calcifications: complete, central, popcorn, concentric rings, and fat- containing nodules	Continue annual screening with LDCT in 12 months
Benign appearance or behavior	Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	**Perifissural nodule**(s)* <10 mm (524 mm^3) **Solid nodule(s):** <6 mm (<113 mm^3), new <4 mm (<34 mm^3) **Part solid nodule(s):** <6 mm total diameter (<113 mm^3) on baseline screening **Nonsolid nodule(s) (GGN):** <30 mm (<14,137 mm^3) OR ≥30 mm (≥14,137 mm^3) and unchanged or slowly growing **Category 3 or 4 nodules unchanged for ≥3 months**	Continue annual screening with LDCT in 12 months
Probably benign	Probably benign finding(s): short-term followup suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	**Solid nodule(s):** ≥6 to <8 mm (≥113 to <268 mm^3) at baseline OR new 4 mm to <6 mm (34 to <113 mm^3) **Part solid nodule(s):** ≥6 mm total diameter (≥113 mm^3) with solid component <6 mm (<113 mm^3) OR new <6 mm total diameter (<113 mm^3) **Nonsolid nodule(s):** (GGN) ≥30 mm (≥14,137 mm^3) on baseline CT or new	6-month LDCT
Suspicious	Findings for which additional diagnostic testing is recommended	4A	**Solid nodule(s):** ≥8 to <15 mm at baseline (≥268 to <1,767 mm^3) OR growing <8 mm (<268 mm^3) OR new 6 to <8 mm (113 to <268 mm^3) **Part solid nodule(s):** ≥6 mm (≥113 mm^3) with solid component ≥6 mm to <8 mm (≥113 to <268 mm^3) OR with a new or growing <4 mm (<34 mm^3) solid component **Endobronchial nodule**	3-month LDCT; PET/CT may be used when there is a ≥8 mm (≥268 mm^3) solid component
Very suspicious	Findings for which additional diagnostic testing and/or tissue sampling is recommended	4B	**Solid nodule(s)** ≥15 mm (≥1,767 mm^3) OR new and growing and ≥8 mm (≥268 mm^3) **Part solid nodule(s)** with a solid component ≥8 mm (≥268 mm^3) OR a new or growing ≥4 mm (≥34 mm^3) solid component	Chest CT with or without contrast, PET/CT and/or tissue sampling depending on the *probability of malignancy and comorbidities. PET/CT may be used when there is a ≥8 mm (≥268 mm^3) solid component. For new large nodules that develop on an annual repeat screening CT, a 1- month LDCT may be recommended to address potentially infectious or inflammatory conditions
		4X	Category 3 or 4 nodules with additional features or imaging findings that increase the suspicion of malignancy†	
Other	Clinically significant or potentially clinically significant findings (nonlung cancer)	S	Modifier: may add on to category 0-4 coding	As appropriate to the specific finding

Adapted from Lung-RADS Version 1.1 Assessment Categories Release date: 2019

Appendix A Table 5. Recommendations for Lung Cancer Screening With LDCT

* Solid nodules with smooth margins, an oval, lentiform or triangular shape, and maximum diameter less than 10 mm or 524 mm^3 (perifissural nodules) should be classified as category 2.
† These include, for example, spiculation, GGN that doubles in size in 1 year, and enlarged lymph nodes.

Abbreviations: CT=computed tomography; GGN=ground glass nodule; LDCT=low-dose computed tomography; NA=not applicable; PET=positron emission tomography.

Some notes on use of Lung-RADS Version 1.1:
1) Nodule mean diameter is calculated by measuring both the long and short axes to one decimal point and reporting mean nodule diameter to one decimal point.
2) Size thresholds: Apply to nodules at first detection, and that grow and reach a higher size category.
3) Growth is defined as an increase in size of >1.5 mm (>2 mm^3).
4) Exam category: Each exam should be coded 0-4 based on the nodule(s) with the highest degree of suspicion.

Appendix A Table 3. Typical Treatment Approaches of SCLC, by Stage[326]

Stage	Treatment Approach
Limited disease	Clinical stage T1-2, N0: Lobectomy + chemotherapy +/− concurrent radiation therapy Clinical stage >T1-2, N0: chemotherapy +/− concurrent or sequential radiation therapy tailored to patient performance status
Extensive disease	Chemotherapy +/− radiation therapy tailored to location and symptoms of metastatic site

Abbreviations: SCLC=small-cell lung cancer; T=tumor.

Appendix A Table 4. Stage of Detected Lung Cancers in LDCT Screening Groups for NLST and NELSON Trials

Stage	NLST (%)	NELSON (%)
Ia	40	58
Ib	10	10
IIa	3.4	5
IIb	3.7	1
IIIa	9.5	14
IIIb	11.7	3
IV	21.7	14

*For reference, the stage distribution based on data from the SEER 18 registry in 2010 is as follows: Ia (11.7%), Ib (8.5%), IIa (1.0%), IIb (3.1%), IIIa (8.5%), IIIb (14.8%), IV (45.1%), occult or unknown (7.3%).[327] Participants in the NLST were younger, better educated, and healthier than individuals of similar age and smoking eligibility in the United States. (SCLC accounted for 7 percent of CT screen-detected cancers in the NELSON trial and 13 percent in NLST).

Abbreviations: LDCT=low-dose computed tomography; NELSON=The Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST=National Lung Screening Trial; SCLC=small cell lung cancer

Appendix A Table 5. Recommendations for Lung Cancer Screening With LDCT

Organization	Year	Target Population	Recommendation and Related Comments	Endorse shared decision making?
American Academy of Family Physicians[44]	2013	Persons with a high risk of lung cancer on the basis of age and smoking history	Insufficient evidence to recommend screening. Screening cannot be recommended on the basis of a single study conducted in major medical centers.	Yes
American Cancer Society[328, 329]	2013	NLST criteria. Excludes life-limiting comorbid conditions, metallic implants or devices in the chest or back, or oxygen requirement	Discussion about screening should be initiated, including benefits, limitations, harms. Recommends only if there is access to a high-volume, high-quality lung cancer screening and treatment center.	Yes
American Lung Association[330]	2015	NLST criteria	Screening with LDCT recommended. Screening should occur in institutions that are able to provide a comprehensive screening program; smoking cessation is the best method of reducing lung cancer risk among those who smoke.	Yes
American Association for Thoracic Surgery[331]	2012	Persons ages 55-79 years with ≥30 pack-year smoking history and persons ages 50-79 years with ≥20 pack-year smoking history and another risk factor for lung cancer* or lung cancer survivor	Annual screening with LDCT. Should be conducted in environments in which there are multidisciplinary teams for managing indeterminate and positive screening scans; desirable to create a program that supports smoking cessation.	Not specified
CHEST Guideline and Expert Panel Report[315]	2018	Asymptomatic persons ages 55-77 years with same smoking history criteria as NLST	Annual screening with LDCT should be offered (weak recommendation, moderate-quality evidence)	Yes
European Union[332]	2017	Lung cancer LDCT programs should use a validated risk stratification approach so that only persons deemed to be at high enough risk are screened†	Screening with LDCT. Management of screen-detected solid nodules should use semi-automatically derived volume measurements and volume-doubling time and should be quality assured. Management of lung nodules by lung cancer multidisciplinary teams. National quality assurance boards should be set up by professional bodies to ensure adherence to all minimum technical standards.	All future screenees should be provided with carefully constructed participant information on the potential benefits and harms to enable them to make an informed decision.
National Comprehensive Cancer Network[43, 333]	2012	NLST criteria and persons age 50 years or older with ≥20 pack-years smoking history and 1 additional risk factor for lung cancer‡	Screening with LDCT. Multidisciplinary screening programs will be helpful; smokers should always be encouraged to quit smoking. It is also reasonable to consider using the PLCOm2012 lung cancer risk calculator to assist in quantifying risk, considering a 1.3% threshold of lung cancer risk (over 6 years).	Patients should have a full understanding of risks and benefits.

Appendix A Table 5. Recommendations for Lung Cancer Screening With LDCT

Organization	Year	Target Population	Recommendation and Related Comments	Endorse shared decision making?
Canadian Task Force on Preventive Health Care[334]	2016	NLST criteria	Screening with LDCT every year up to 3 consecutive years (weak, low-quality evidence). Screening should only be performed in health care settings with access to expertise in early diagnosis and treatment of lung cancer.	Yes, discussion about benefits and harms, including false-positive screens, adverse effects of invasive followup testing, and overdiagnosis

* Examples of additional risk factors, as specified by the American Association for Thoracic Surgery, include COPD, environmental or occupational exposure, prior cancer or radiation therapy, and genetic predisposition or family history.
† No specific model is recommended.
‡ Examples of additional risk factors, as specified by the National Comprehensive Cancer Network, include radon exposure, occupational exposure, history of cancer, family history of lung cancer, COPD, and pulmonary fibrosis.

Abbreviations: COPD=chronic obstructive pulmonary disease; CT=computed tomography; LDCT=low-dose computed tomography; NLST=National Lung Screening Trial.

CQ 1. What Are the Barriers to Implementing Lung Cancer Screening and Surveillance in Clinical Practice in the United States (e.g., Barriers to Shared Decision Making, Systematically Eliciting and Documenting a Detailed Smoking History, Systems for Tracking Nodules and Followup, and Availability of Appropriate LDCT Protocols)?

Introduction

Since the 2013 USPSTF statement on lung cancer screening, multiple expert groups and specialty societies have published consensus-based guidance documents on screening implementation.[315, 335-339] Common among these guidance statements is an acknowledgement that implementation of lung cancer screening is a highly complex process requiring multiple, inter-connected steps. There is also a growing body of literature aimed at understanding barriers to implementation of lung cancer screening. A recent perspective article offered a high-level summary of implementation barriers using a multi-level (patient, provider, and system-level) framework (**Table 6**).[340] This contextual question section is not on a comprehensive account of the many clinical and technical aspects of screening implementation. Rather, it highlights some of the salient barriers to the appropriate and effective implementation of lung cancer screening that have arisen since the 2013 USPSTF statement. These include barriers to SDM, systematic identification of screen-eligible patients, systems for tracking nodules and followup, and availability of LDCT protocols.

Barriers to Shared Decision Making

Screening Guidelines and SDM

Lung cancer screening guidelines are virtually unanimous in asserting that informed and SDM should occur before a patient proceeds with screening.[315, 334, 335, 341] The American Cancer Society recommends that "a process of informed and SDM with a clinician related to the potential benefits, limitations, and harms associated with screening for lung cancer with low-dose computed tomography should occur before any decision is made to initiate lung cancer screening."[328] The 2013 USPSTF recommendation stated that "the decision to begin screening should be the result of a thorough discussion of the possible benefits, limitations, and known and uncertain harms."[1] In 2014, the CMS coverage decision for lung cancer screening was issued that contained several stipulations including a requirement for "a lung cancer screening counseling and shared decision-making visit." Required elements of this visit included "the use of one or more decision aids, to include benefits, harms, followup diagnostic testing, over-diagnosis, false positive rate, and total radiation exposure."[40]

SDM in Practice

Unfortunately, emerging evidence raises concerns that SDM in practice may be far from what is intended by guidelines. A recent study found that CMS-required SDM visits were evident in just 10 percent of Medicare beneficiaries who had a screening LDCT in 2016.[342] Another study analyzed transcribed recordings of discussions between community physicians (primary care physicians and pulmonologists) and patients about initiating lung cancer screening.[343] In these discussions (n=14), which were identified by searching a large database, SDM quality was universally poor and discussion of screening harms was essentially nonexistent. Average time for screening discussion was 57 seconds and was typically focused on insurance coverage. There was no evidence that decision aids were used.

Competing Demands

Systematic reviews have found that SDM is difficult to implement well in practice, regardless of clinical context.[344] Factors associated with higher quality SDM include time (duration of encounter) and decision support interventions (including decision aids). Since the USPSTF 2013 recommendation, multiple studies have identified competing demands and limited time available to conduct SDM during clinical encounters as a central barrier to implementing SDM.[37, 345-349]

Patient Perceptions of Screening

Adding to the challenge of SDM implementation is evidence that patient's "baseline" perceptions of the benefits and harms of lung cancer screening diverge from what the evidence shows. In one study of (n=50) screen-eligible patients who had not yet seen a decision aid overestimated the likelihood of benefitting from screening by orders of magnitude. Patients also had poor awareness of potential harms of screening.[42] In another study involving focus groups of screening eligible patients (n=45), participants expressed surprise that the magnitude of their lung cancer risk and benefits of screening were lower than expected.[345] These studies suggest that patient's baseline perceptions are systematically inaccurate (i.e., biased) in favor of screening. These biases are not unique to lung cancer screening, and there is robust evidence that patients, members of the public, and clinicians typically overestimate the benefits and underestimate the harms of cancer screening tests.[350-352]

Such biases pose challenges for implementing SDM about screening in practice. Primary care physicians, who routinely discuss cancer screening with patients, recognize that initiating a conversation about the availability of a lung cancer screening test will provoke immediate assumptions on the part of the patient. For meaningful SDM, a provider who initiates such a discussion about lung cancer screening must be prepared to provide balanced information that calibrates patient perceptions and expectations to reflect what is known.

Although providing screen-eligible patients individualized, quantitative risk information is (theoretically) ideal, a first order concern is implementing processes that offer patients a) a reasonable sense of the benefits and harms of screening, including approximate likelihoods for these outcomes; b) an understanding that the screening decision involves tradeoffs between these

benefits and harms; and c) a recognition that the "weights" placed on avoiding harms relative to benefits should reflect the values of the patient him/herself.

Timing and Context of SDM

Experts have expressed a range of views about whether SDM about lung cancer screening should occur in primary care, subspecialty care, and/or within centralized screening programs.[353, 354] The potential benefits of SDM in a subspecialized LDCT screening context are the increased chances that providers will be knowledgeable about lung cancer screening, have time to dedicate to the issue of screening, and use established workflows that employ decision support tools. On the other hand, potential downsides of conducting SDM in centralized screening centers is that patients are likely to assume that a referral to a lung cancer screening program is a referral for the screening procedure itself rather than to participate in process by which they will decide whether screening is right for them. Thus, by the time the patient reaches the screening center context, absent a good prior discussion, it is likely they will arrive with inaccurate perceptions of the benefits and harms and will have already decided to be screened.[353-356]

Emerging evidence lends support to the idea that the timing and context of the SDM process (i.e., primary care vs. referral setting) can influence patient decisions. One study in a primary care population of screening-eligible patients (n=50) found viewing a video decision aid improved understanding of the nature and magnitude of the harms and benefits of screening.[42] When asked to indicate their screening preferences, 50 percent preferred screening while the other 50 percent did not. In another study of screen-eligible primary care patients (n=81) who were reached through an electronic health record portal and viewed a lung cancer screening decision aid, screening preferences were again heterogeneous: 30 percent desired screening, 44 percent were "unsure," and 26 percent declined screening.[357] In contrast to these studies in primary care context, a study of patients attending a tertiary referral lung cancer screening program (n=423) who received robust patient education and decision support that included decision aid viewing, 95 percent proceeded to have a screening LDCT.[358] In sum, there is evidence that, in primary care populations, informed preferences about lung cancer screening are heterogeneous (i.e., that the decision is, in fact, "preference sensitive"). SDM conducted only after a patient reaches a lung cancer screening center may miss the "decision window" during which patients actually make the decision.

System and Personnel Barriers to Identifying Eligible Populations (Detailed Smoking Histories)

One challenge to population or system level implementation in identifying populations eligible for screening is that detailed, patient-level smoking histories, including average number of cigarettes smoked per day, start dates, and quit dates, are not readily available within the electronic health record.

Moreover, smoking behavior is dynamic, meaning that these data need to be periodically verified for accuracy. Clinical demonstration studies suggest that, even with additional resources dedicated to eliciting and documenting smoking histories, these data fields often still have incomplete or inaccurate information. In the VHA implementation project, substantial resources

were dedicated to having nurses elicit and enter these data. Despite this, among 93,033 patients who met basic age and comorbidity criteria, a total of 36,555 patients (39.3%) were missing necessary smoking history data (or the tobacco pack-years were improperly calculated) needed to systematically identify screening-eligible patients.[38] In 1-year, single-site primary care implementation project, nurses and support staff were able to elicit and document smoking histories in 53 percent of ever smokers between ages 55 and 80 years.[359]

Availability of Appropriate LDCT Protocols

Another potential implementation issue is whether radiology facilities that are capable of providing LDCT scanning are available. Early studies published soon after the 2013 USPSTF statement raised concerns about limited capacity.[360] However, the number of lung cancer screening centers is growing rapidly. In 2014, there were 203 screening centers certified by the American College of Radiology (ACR) in the United States. By 2017, that number had increased to 1,748.[361] According to the ACR website, there are 2,013 ACR-certified centers as of April 2019.[362]

Systems for Tracking Nodules and Ensuring Followup (Patient Coordination)

The availability of centers that are certified to *perform* LDCT screening and to *report* results to a national registry should be distinguished from the availability of infrastructure needed to *track and manage* individuals with screen-detected lung nodules. There is broad expert consensus that screen-detected lung nodules should be managed based on established algorithms,[315, 335-339] which call for regular and timely surveillance of screen-detected nodules. Operationalizing surveillance of lung nodules for a large, high-risk population will require robust longitudinal tracking and patient coordination systems for the large numbers of individuals with lung nodules. The VHA Lung Cancer Screening Demonstration Project (LCSDP) found this aspect of implementation to be challenging and complex, as most patients screened had findings that required followup. Specifically, 56 percent of screened patients had one or more nodules that required tracking and 41 percent had incidental findings. Implementation required substantial resources for manual abstraction of patient information from records and the creation of dedicated tracking and patient coordination systems.[38]

While there is no comprehensive accounting of patient coordination and tracking systems in the United States, surveys and interviews have found that both primary care physicians and subspecialists have concerns about whether there is sufficient personnel and tracking infrastructure needed for screening implementation.[37, 345-349, 363]

Out-of-Pocket Costs for Followup of Screen-Detected Findings

ACA insurance plans are required to cover LDCTs done for *screening*. However, patients with screen-detected nodules enter diagnostic and surveillance pathways involving evaluations, imaging, and procedures that are not considered screening and are subject to copays and deductibles. Since the 2013 USPSTF statement, multiple studies in both patients and providers

have identified the issue that the costs of followup testing after positive screening results will lead to financial harm for patients.[37, 346-349, 364, 365] Even if less aggressive nodule categorization approaches (e.g., Lung-RADS) are used, the number of patients who will enter surveillance pathways for screen-detected nodules is large. Given that high-deductible insurance plans among low and middle-income Americans, the issue of patient cost as a barrier to lung cancer screening implementation requires further study.[366]

CQ 2a. Are the Participants of Randomized, Controlled Trials of Lung Cancer Screening (e.g., NLST) That Reported a Reduction in All-Cause or Lung Cancer Mortality Representative of Screening-Eligible U.S. Adults (Based on NLST Criteria or USPSTF Recommendations)?

b. How Do the 5-Year Survival Rate and Life Expectancy of Persons Eligible for Lung Cancer Screening in the United States (Based on NLST Criteria or USPSTF Recommendations) Compare With Those of NLST Participants?

c. Are the Settings and Providers in Randomized, Controlled Trials of Lung Cancer Screening (e.g., NLST) That Reported a Reduction in All-Cause or Lung Cancer Mortality Representative of U.S. Health Care Settings and Providers?

The Discussion of this report describes the applicability of NLST and other included studies. Briefly, NLST participants were younger, more highly educated, and less likely to be current smokers than the U.S. screening-eligible population.[367] Furthermore, the NLST was mainly conducted at large academic centers, potentially limiting its applicability to community-based practice (e.g., because of challenges with implementation, level of expertise). Many of the trial centers are well-recognized for expertise in radiology as well as cancer diagnosis and treatment.[32] Community centers may be less equipped for screening programs and for treatment of lung cancers identified by screening. For example, the NLST publication noted that mortality associated with surgical resection of lung cancer was much lower in the trial than that reported for the U.S. population (1% vs. 4%).[32, 296]

A study using data from the 2012 Health and Retirement Study (HRS) (a national survey of adults 50 and older) evaluated comorbidities, life expectancy, smoking history, and other characteristics in the screening-eligible population and in NLST participants; it reported a lower 5-year survival rate and life expectancy in the screening-eligible persons compared with NLST participants (87% vs. 93%, $p<0.001$, and 18.7 years vs. 21.2 years, respectively).[25] Screening-eligible HRS respondents were older, more likely to be current smokers, and more likely to have been diagnosed with comorbidities than NLST participants. The authors concluded that the

general U.S. population eligible for lung cancer screening is probably less likely to benefit from early detection compared with the NLST participants because they face a high risk of death from competing causes, such as heart disease, diabetes, or stroke.

CQ 3. Does Screening for Lung Cancer With LDCT Have Unintended Benefits From Detecting Incidental Findings (e.g., Coronary Artery Calcium, Chronic Obstructive Pulmonary Disease, or Extrapulmonary Nodules) Leading to Interventions That Improve Health Outcomes?

Common incidental findings identified in this systematic review included coronary artery calcification, aortic aneurysms, emphysema, infections, and masses or nodules (e.g., of the thyroid or pancreas), among others. There is no trial evidence to indicate that screening with LDCT for such findings has greater unintended benefit than unintended harm. The USPSTF portfolio includes evidence reviews and recommendations covering the evidence on potential benefits and harms of screening for many of these conditions/findings in asymptomatic persons. The evidence reviews have resulted in I statements (i.e., insufficient evidence) and D recommendations (i.e., harm of screening greater than benefit). For example, the USPSTF recommendation statement on nontraditional cardiovascular risk factors concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for coronary artery calcium (CAC) in asymptomatic adults to prevent CVD events.[368] Further, USPSTF had D recommendations for screening for chronic obstructive pulmonary disease (COPD),[369] thyroid cancer,[370] and pancreatic cancer in asymptomatic adults. Regarding screening for aneurysms, USPSTF recommends one-time screening for abdominal aortic aneurysm (AAA) with ultrasonography in men ages 65 to 75 years who have ever smoked[371]; an update is in progress.[372] There is no trial evidence to indicate greater benefit than harm for using LDCT to screen for aneurysms (thoracic or abdominal).

CQ 4. What Is the Effectiveness of Smoking Cessation Intervention Among Patients Receiving LDCT Screening?

The provision of smoking cessation interventions with LDCT screening is an opportunity to improve health outcomes. In the NLST, screening with LDCT combined with smoking abstinence of 15 years provided the greatest reduction in lung cancer mortality (comparing, for example, with screening with LDCT and current smoking).[373] The Centers for Medicare & Medicaid Services also requires that smokers who undergo screening receive counseling on smoking cessation so as not to mistake screening as either a substitute for cessation or a confirmation that it is acceptable to continue smoking if the screening result is normal.[374] The USPSTF recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and U.S. Food and Drug Administration (FDA)–approved pharmacotherapy for cessation to adults who use tobacco.[375]

Two systematic reviews focused on this contextual question.[376, 377] Assessment of these reviews using AMSTAR-2 criteria indicates at least moderate confidence in the results.[378] Neither systematic review conducted meta-analyses because of heterogeneity of interventions and other factors. The first systematic review[376] included six studies published through July 1, 2015: three randomized, controlled trials (RCTs) (with a total of 1473 participants) and three uncontrolled studies (total 7,333 participants).[376] Two of the RCTs compared the use of written self-help materials with internet or computer-based tailored self-help materials for smoking cessation intervention among patients receiving lung cancer screening and found no statistically significant difference in abstinence rates between groups.[379, 380] The third RCT evaluated the effect of smoking cessation interventions before and after LDCT and found that smoking intervention before LDCT led to numerically higher abstinence rates at 4 months (33.3 vs. 22.2%) and 6 months (22.2% vs. 11.1%) after treatment,[381] although statistical testing was not provided for the comparison between groups (a subsequently published systematic review conducted its own statistical tests for those comparisons and reported no significant difference between groups, p=1.0[377]). Continuous abstinence rates in uncontrolled studies ranged from 19.8 percent at 1-year followup[382] to 57.1 percent at 6-months followup[383] across included studies. No rating of the risk of bias of included studies was reported. The authors reported that their findings suggest that there are benefits to implementing smoking cessation interventions in lung cancer screening programs, which may represent a teachable moment to quit smoking.[376]

The second systematic review[377]included nine studies published through May 1, 2018. It restricted eligibility to RCTs and observational studies with a comparison group, which excluded the three single-arm studies that were in the other[376] systematic review. The included five RCTs (with a total of 1,620 participants) and four observational studies (total 5,114 participants) were rated as poor to fair quality with significant potential for bias and limited generalizability.[377] Though the studies provided insufficient evidence to support a particular approach to smoking cessation interventions in the LDCT screening setting, the authors suggested that more intensive interventions (e.g., multiple counseling sessions) appear to be more effective approaches to smoking cessation. Table 7 summarizes the five RCTs included in the review. Sample sizes ranged from 18 to 1,284, with three of the studies having fewer than 100 participants. The largest study (with 1,284 participants) was part of the NELSON lung cancer screening trial.[380] Only one of the studies found a statistically significant difference in smoking cessation outcomes between groups, with an intervention of six weekly telephone counseling calls compared to a list of resources.[384] Two of the studies used two or fewer counseling sessions as the intervention, while the other two distributed tailored smoking cessation resources. Four of the comparison groups for the RCTs distributed nontailored resources; the other altered the timing of smoking cessation counseling sessions. The authors of the systematic review conducted a search of ongoing trials, finding 11 ongoing RCTs assessing smoking cessation interventions in the context of LDCT screening.[377]

In sum, limited evidence exists to establish the effectiveness of smoking cessation interventions in lung cancer screening programs. However, this is an active area of research, with numerous ongoing trials comparing intervention methods. Further research to determine components of smoking cessation interventions that can optimize outcome by testing different modalities in lung cancer screening programs and to identify strategies to effectively integrate smoking cessation interventions in lung cancer screening sites have also been suggested.

Appendix A Table 6. Summary of Multilevel Barriers to Effective Lung Cancer Screening

Patient-level barriers
• Competing needs and demands for health care • Cost • Fear (e.g., procedures, diagnosis, treatment) • Lack of awareness • Lack of interest due to stigma associated with smoking • Limited access to care due to financial or social factors • Limited information and misinformation • Logistical issues (e.g., inconvenience, time) • Mistrust of the health care system and/or health care • Nihilism
Provider-level barriers
• Competing demands for time • Evolving attitudes about the effectiveness of screening • Lack of awareness • Limited information and misinformation • Limited training in SDM • Nihilism related to treatment of lung cancer • Requirement for behavior change (adaptive challenge)
System-level barriers
• Lack of support from health system leaders • Limited resources to support screening, including equipment, personnel, and information technology resources • Competing demands for limited resources (e.g., other screening programs or preventive health interventions) • Uncertain return on investment • Complexity of implementation (requires multidisciplinary collaboration) o Conflicting upper age range recommendations for screening o Identification of screening-eligible patients (gaps in smoking status data)

Source: Carter-Harris L, Gould MK. Multilevel barriers to the successful implementation of lung cancer screening: why does it have to be so hard? *Ann Am Thorac Soc*. 2017 Aug;14(8):1261-5. doi: 10.1513/AnnalsATS.201703-204PS. PMID: 28541749.[340]

Appendix A Table 7. Summary of Randomized, Controlled Trials in the Systematic Review From 2019

Author, Year	Trial	Sample Size	Intervention	Comparison	Findings
Clark, 2004[379]	NA	171	Internet-based resources (10 links).	Written self-help materials from the NCI.	No significant difference in 12 month quit rates or change in readiness to quit. Increased number of quit attempts in intervention group (p=0.011).
Aalst, 2012[380]	NELSON	1284	Computer-generated, tailored self-help material based on input of individual smoking behaviors and history.	Standard brochure with smoking cessation information for different stages of readiness to quit.	No significant difference in point prevalence, quit attempts, or prolonged smoking abstinence at 24 months followup.
Ferketich, 2012[381]	NA	18	Smoking cessation counseling with a medical oncologist occurring before LDCT performed followed by 12-week tobacco dependence protocol.	Smoking cessation counseling with a medical oncologist occurring after LDCT performed followed by 12-week tobacco dependence protocol.	No significant difference in abstinence among those who received counseling before LDCT and those who received counseling after LDCT at 4 months and 6 months.
Marshall, 2016[385]	NA	55	Single face-to-face tailored counseling session with take-home audio education materials, printed materials, and telephone helpline referral.	Nontailored printed smoking cessation materials and telephone helpline referral.	No significant difference in quit rates at 12 months for patients receiving counseling intervention compared to the control group.
Taylor, 2017[384]	NA	92	Resources list plus 6 weekly, proactive counseling calls.	Resource list: Booklet, website, contact information for local resources, text messaging link.	Higher 7-day point prevalence cessation at 3-months in patients who received telephone counseling.

Abbreviations: LDCT=low-dose computed tomography; NA=not applicable; NCI=National Cancer Institute; NELSON=Dutch-Belgian Randomized Lung Cancer Screening Trial.

Screening Searches
PubMed, 4-30-18

Search	Query	Items Found
#1	Search (“Lung Neoplasms”[MeSH] OR NSCLC[tiab] OR “lung cancer”[tiab] OR “lung cancers” [tiab] OR “lung-cancer”[tiab] OR “lung malignancy”[tiab] OR “lung malignancies”[tiab] OR “lung nodule”[tiab] OR “lung nodules” [tiab] OR “pulmonary nodule”[tiab] OR “pulmonary nodules”[tiab] OR “lung mass”[tiab] OR “lung masses”[tiab] OR (“Squamous Cell Carcinoma”[MeSH] OR Adenocarcinoma[MeSH]) and (Lung[MeSH] OR Lung Diseases[MeSH]))	209038
#2	Search (“Mass Screening”[MeSH] OR screen*[tw] OR “Early Diagnosis”[MeSH] OR “Tomography, X-Ray Computed”[Mesh] OR “CT scan”[tiab] OR “CT scans”[tiab] OR “CAT scan”[tiab] OR “CAT scans”[tiab] OR “spiral CT”[tiab] OR “spiral computed tomography”[tiab] OR “low-dose computed tomography”[tiab] OR LDCT[tiab] OR ((early[tiab] or earlier[tiab] or earliest[tiab]) AND (detect*[tiab] or diagnos*[tiab] or discover*[tiab] or find[tiab] or finding[tiab])))	1561323
#3	Search (#1 and #2)	33537
#4	Search (DANTE[tiab] OR “Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays”[All Fields] OR DLCST[tiab] OR “Danish Lung Cancer Screening Trial”[tiab] OR ITALUNG[tiab] OR “Italian Lung Cancer Screening Trial”[All Fields] OR LUSI[tiab] OR “Lung Cancer Screening Intervention”[All Fields] OR MILD[tiab] OR “Multicentric Italian Lung Detection”[All Fields] OR NELSON[tiab] OR “Dutch-Belgian Lung Cancer Screening trial”[All Fields] OR NLST[tiab] OR “National Lung Screening Trial”[All Fields])	306902
#5	Search (#1 and #4)	2661
#6	Search (#3 or #5)	35398
#7	Search (#3 or #5) Filters: Publication date from 2012/01/01 to 2018/12/31	12321
#8	Search (“Risk prediction model”[tw] OR “Risk prediction models”[tw] OR “Risk Assessment”[MeSH] OR “risk assessment”[tw] OR “risk model”[tw] OR “risk models”[tw] OR “Decision Support Techniques”[MeSH] OR “Decision Support Systems, Clinical”[Mesh] OR “clinical prediction”[tw] OR “Logistic Models”[MeSH] OR microsimulation*[tw] OR “simulation model”[tw] OR “simulation models”[tw] OR “Assessment tool”[tw] OR “Assessment tools”[tw] OR “prediction score”[tw] OR “Risk Factors”[MeSH] OR “Predictive Value of Tests”[MeSH] OR “Sensitivity and Specificity”[MeSH] OR (Predict*[tw] AND (model*[tw] OR outcome*[tw] OR risk*[tw] OR rule[tw] OR rules[tw])) OR “risk-targeted”[tw] OR “mortality risk”[tw])	2073965
#9	Search (#1 and #8)	26417
#10	Search (#1 and #8) Filters: Publication date from 2014/04/01 to 2018/12/31	6640
#11	Search (#7 or #10)	16840
#12	Search (#7 or #10) Filters: Humans	16584
#13	Search (#7 or #10) Filters: Humans; English	15409
#14	Search (#7 or #10) Filters: Humans; English; Child: birth-18 years	605
#15	Search (letter[pt] OR newspaper article[pt] OR editorial[pt] OR comment[pt])	1642710
#16	Search (#13 NOT #14)	14804
#17	Search (#16 NOT #15)	14186
#18	Search (“systematic review”[ti] OR “meta-analysis”[pt] OR “meta-analysis”[ti] OR “systematic literature review”[ti] OR “this systematic review”[tw] OR (“systematic review”[tiab] AND review[pt]) OR meta synthesis[ti] OR “meta synthesis”[ti] OR “cochrane database syst rev”[ta])	178836
#19	Search (#17 and #18)	**485**
#20	Search (“Randomized Controlled Trial”[Publication Type] OR “Single-Blind Method”[MeSH] OR “Double-Blind Method”[MeSH] OR “Random Allocation”[MeSH] OR ((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract]))	618965
#21	Search (#17 and #20)	**462**
#22	Search (“Case-Control Studies”[MeSH] OR “Cohort Studies”[MeSH] OR “Epidemiologic Studies”[MeSH] OR “Follow-Up Studies”[MeSH] OR “Evaluation Studies”[Publication Type] OR “Program Evaluation”[MeSH] OR “observational study”[tw] OR “observational studies”[tw] OR “Cohort Studies”[MeSH] OR “Comparative Study”[pt] OR “Validation Studies”[pt] OR “Prospective Studies”[MeSH] OR “cohort”[tw] OR “case control”[tw])	4054856
#23	Search (#17 and #22)	**5869**

Appendix B1. Original Search Strategies and Update Searches

Cochrane Library, 5-2-2018

ID	Cochrane Library Search	Hits
#1	[mh “Lung Neoplasms”] or NSCLC:ti,ab or “lung cancer”:ti,ab or “lung cancers”:ti,ab or “lung-cancer”:ti,ab or “lung malignancy”:ti,ab or “lung malignancies”:ti,ab or “lung nodule”:ti,ab or “lung nodules”:ti,ab or “pulmonary nodule”:ti,ab or “pulmonary nodules”:ti,ab or “lung mass”:ti,ab or “lung masses”:ti,ab or (([mh “Squamous Cell Carcinoma”] or [mh Adenocarcinoma]) and ([mh Lung] or [mh “Lung Diseases”]))	13223
#2	[mh “Mass Screening”] or screen*:kw or [mh “Early Diagnosis”] or [mh “Tomography, X-Ray Computed”] or “CT scan”:ti,ab or “CT scans”:ti,ab or “CAT scan”:ti,ab or “CAT scans”:ti,ab or “spiral CT”:ti,ab or “spiral computed tomography”:ti,ab or “low-dose computed tomography”:ti,ab or LDCT:ti,ab or ((early:ti,ab or earlier:ti,ab or earliest:ti,ab) and (detect*:ti,ab or diagnos*:ti,ab or discover*:ti,ab or find:ti,ab or finding:ti,ab))	42901
#3	#1 and #2	1293
#4	DANTE:ti,ab or “Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays” or DLCST:ti,ab or “Danish Lung Cancer Screening Trial”:ti,ab or ITALUNG:ti,ab or “Italian Lung Cancer Screening Trial” or LUSI:ti,ab or “Lung Cancer Screening Intervention” or MILD:ti,ab or “Multicentric Italian Lung Detection” or NELSON:ti,ab or “Dutch-Belgian Lung Cancer Screening trial” or NLST:ti,ab or “National Lung Screening Trial”:kw	43092
#5	#1 and #4	541
#6	#3 or #5	1615
#7	#6 Publication Year from 2012 to 2018	916
#8	“Risk prediction model”:ti,ab,kw or “Risk prediction models”:ti,ab,kw or [mh “Risk Assessment”] or “risk assessment”:ti,ab,kw or “risk model”:ti,ab,kw or “risk models”:ti,ab,kw or [mh “Decision Support Techniques”] or [mh “Decision Support Systems, Clinical”] or “clinical prediction”:ti,ab,kw or [mh “Logistic Models”] or microsimulation*:ti,ab,kw or “simulation model”:ti,ab,kw or “simulation models”:ti,ab,kw or “Assessment tool”:ti,ab,kw or “Assessment tools”:ti,ab,kw or “prediction score”:ti,ab,kw or [mh “Risk Factors”] or [mh “Predictive Value of Tests”] or [mh “Sensitivity and Specificity”] or (Predict*:ti,ab,kw and (model*:ti,ab,kw or outcome*:ti,ab,kw or risk*:ti,ab,kw or rule:ti,ab,kw or rules:ti,ab,kw)) or “risk-targeted”:ti,ab,kw or “mortality risk”:ti,ab,kw	102435
#9	#1 and #8	1595
#10	#9 Publication Year from 2014 to 2018	637
#11	#7 or #10	1385
#12	child:ti or child:ab or child:kw or children:ti or children:ab or children:kw or adolescen*:ti or adolescen*:ab or adolescen*:kw or teen:ti or teen:ab or teen:kw or teens:ti or teens:ab or teens:kw or teenage*:ti or teenage*:ab or teenage*:kw or youth:ti or youth:ab or youth:kw or youths:ti or youths:ab or youths:kw or pediatric*:ti or pediatric*:ab or pediatric*:kw or paediatric*:ti or paediatric*:ab or paediatric*:kw or boys:ti or boys:ab or boys:kw or girls:ti or girls:ti or girls:kw	191065
#13	#11 not #12	1353
#14	#13 in Cochrane Reviews (Reviews and Protocols) and Other Reviews	46
#15	“randomized controlled trial”:pt or “randomized controlled trial”:ti or “randomized controlled trial as topic”:pt or “single-blind method”:pt or “double-blind method”:pt or “random allocation”:pt	466945
#16	#13 and #15	387
#17	[mh “Case-Control Studies”] or [mh “Cohort Studies”] or [mh “Epidemiologic Studies”] or [mh “ Follow-Up Studies “] or [mh “Seroepidemiologic Studies”] or “Evaluation Studies”:pt or [mh “Program Evaluation”] or “observational study” or “observational studies” or [mh “case-control studies”] or “comparative study”:pt or “validation studies”:pt or [mh “Prospective Studies”] or “cohort” or “case control”	305186
#18	(#13 and #17) not (#14 or #16) in Methods Studies, Technology Assessments, Economic Evaluations and Cochrane Groups	4

Intervention searches
PubMed, 5-1-2018

Search	Query	Items Found
#4	Search (“Carcinoma, Non-Small-Cell Lung”[MeSH] OR “non-small-cell lung cancer”[All Fields] OR NSCLC[tiab] OR (“non small cell”[tiab] AND lung*[tiab] AND cancer*[tiab]) OR “Carcinoma, Squamous Cell”[Mesh] OR Adenocarcinoma[MeSH] OR “Carcinoma, Large Cell”[MeSH])	493740
#5	Search ((stag* AND (one or “1” or I or two or “2” or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb)))	836529
#6	Search (((early or earlier or earliest) AND (discover* or found or find or finding or uncover* or diagnos* or detect* or stage* or staging)))	880795
#7	Search (#5 or #6)	1496819
#8	Search (#4 and #7)	106951
#9	Search (“Margins of Excision”[Mesh] OR Pneumonectomy OR Lobectomy OR (resection* and lung*[tw]))	38216
#10	Search (#8 and #9)	3942
#11	Search (letter[pt] OR newspaper article[pt] OR editorial[pt] OR comment[pt])	1643073
#12	Search (#10 not #11)	3885
#13	Search (#10 not #11) Filters: Humans	3647
#14	Search (#10 not #11) Filters: Humans; English	2921
#15	Search (#10 not #11) Filters: Publication date from 2012/01/01 to 2018/12/31; Humans; English	1253
#16	Search (#10 not #11) Filters: Publication date from 2012/01/01 to 2018/12/31; Humans; English; Child: birth-18 years	45
#17	Search (#15 NOT #16)	1208
#18	Search (“systematic review”[ti] OR “meta-analysis”[pt] OR “meta-analysis”[ti] OR “systematic literature review”[ti] OR “this systematic review”[tw] OR (“systematic review”[tiab] AND review[pt]) OR meta synthesis[ti] OR “meta synthesis”[ti] OR “cochrane database syst rev”[ta])	178955
#19	Search (#17 and #18)	29
#20	Search (“Randomized Controlled Trial”[Publication Type] OR “Single-Blind Method”[MeSH] OR “Double-Blind Method”[MeSH] OR “Random Allocation”[MeSH] OR ((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract]))	619155
#21	Search (#17 and #20)	41
#22	Search (“Case-Control Studies”[MeSH] OR “Cohort Studies”[MeSH] OR “Epidemiologic Studies”[MeSH] OR “Follow-Up Studies”[MeSH] OR “Evaluation Studies”[Publication Type] OR “Program Evaluation”[MeSH] OR “observational study”[tw] OR “observational studies”[tw] OR “Cohort Studies”[MeSH] OR “Comparative Study”[pt] OR “Validation Studies”[pt] OR “Prospective Studies”[MeSH] OR “cohort”[tw] OR “case control”[tw])	4056042
#23	Search (#17 and #22)	842

Appendix B1. Original Search Strategies and Update Searches

Cochrane Library, 5-2-2018

ID	Search	Hits
#1	[mh “Carcinoma, Non-Small-Cell Lung”] or “non-small-cell lung cancer” or NSCLC:ti,ab or (“non small cell”:ti,ab and lung*:ti,ab and cancer*:ti,ab) or [mh “Carcinoma, Squamous Cell”] or [mh Adenocarcinoma] or [mh “Carcinoma, Large Cell”]	15389
#2	stag* and (one or “1” or I or two or “2” or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb)	62403
#3	(early or earlier or earliest) and (discover* or found or find or finding or uncover* or diagnos* or detect* or stage* or staging)	51466
#4	#2 or #3	96758
#5	#1 and #4	6205
#6	([mh “Margins of Excision”] or Pneumonectomy or Lobectomy or (resection* and lung*:ti,ab,kw))	2545
#7	#5 and #6	540
#8	letter:pt or newspaper article:pt or editorial:pt or comment:pt	9229
#9	#7 not #8	539
#10	child:ti or child:ab or child:kw or children:ti or children:ab or children:kw or adolescen*:ti or adolescen*:ab or adolescen*:kw or teen:ti or teen:ab or teen:kw or teens:ti or teens:ab or teens:kw or teenage*:ti or teenage*:ab or teenage*:kw or youth:ti or youth:ab or youth:kw or youths:ti or youths:ab or youths:kw or pediatric*:ti or pediatric*:ab or pediatric*:kw or paediatric*:ti or paediatric*:ab or paediatric*:kw or boys:ti or boys:ab or boys:kw or girls:ti or girls:ti or girls:kw	190954
#11	#9 not #10	528
#12	#11 Publication Year from 2012 to 2018, in Cochrane Reviews, Other Reviews	**30**
#13	“randomized controlled trial”:pt or “randomized controlled trial”:ti or “randomized controlled trial as topic”:pt or “single-blind method”:pt or “double-blind method”:pt or “random allocation”:pt	466999
#14	#11 and #13 Publication Year from 2012 to 2018	**59**
#15	[mh “Case-Control Studies”] or [mh “Cohort Studies”] or [mh “Epidemiologic Studies”] or [mh “ Follow-Up Studies “] or [mh “Seroepidemiologic Studies”] or “Evaluation Studies”:pt or [mh “Program Evaluation”] or “observational study” or “observational studies” or [mh “case-control studies”] or “comparative study”:pt or “validation studies”:pt or [mh “Prospective Studies”] or “cohort” or “case control”	305126
#16	#11 and #15 Publication Year from 2012 to 2018, in Methods Studies, Technology Assessments, Economic Evaluations and Cochrane Groups	**2**

SBRT-SABR Patch Searches
PubMed, 8-10-2018

Search	Query	Items Found
#1	Search (“Carcinoma, Non-Small-Cell Lung”[MeSH] OR “non-small-cell lung cancer”[All Fields] OR NSCLC[tiab] OR (“non small cell”[tiab] AND lung*[tiab] AND cancer*[tiab]) OR “Carcinoma, Squamous Cell”[Mesh] OR Adenocarcinoma[MeSH] OR “Carcinoma, Large Cell”[MeSH])	500717
#2	Search stag* AND (one or “1” or I or two or “2” or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb)	851242
#3	Search (early or earlier or earliest) AND (discover* or found or find or finding or uncover* or diagnos* or detect* or stage* or staging)	896718
#4	Search (#2 or #3)	1523639
#5	Search (#1 and #4)	108779
#6	Search “Radiosurgery”[Mesh] OR “stereotactic body radiotherapy” OR SBRT[tw] OR “stereotactic body RT” OR “Stereotactic RT” OR “stereotactic ablative radiotherapy” OR SABR[tw]	14808
#7	Search (#5 and #6)	1086
#8	Search letter[pt] OR newspaper article[pt] OR editorial[pt] OR comment[pt]	1666509
#9	Search (#7 not #8)	1050
#10	Search ((#9 AND Humans[Mesh:NOEXP]) OR (#9 NOT Animals[Mesh:NOEXP]))	1048
#11	Search ((#9 AND Humans[Mesh:NOEXP]) OR (#9 NOT Animals[Mesh:NOEXP])) Sort by: Author Filters: English	994
#12	Search ((#9 AND Humans[Mesh:NOEXP]) OR (#9 NOT Animals[Mesh:NOEXP])) Sort by: Author Filters: Publication date from 2014/01/01 to 2018/12/31; English	580
#13	Search (((“systematic review”[ti] OR “meta-analysis”[pt] OR “meta-analysis”[ti] OR “systematic literature review”[ti] OR “this systematic review”[tw] OR (“systematic review”[tiab] AND review[pt]) OR meta synthesis[ti] OR “meta synthesis”[ti] OR “cochrane database syst rev”[ta]))	186300
#14	Search (#12 and #13)	**22**
#15	Search “Randomized Controlled Trial”[Publication Type] OR “Single-Blind Method”[MeSH] OR “Double-Blind Method”[MeSH] OR “Random Allocation”[MeSH] OR ((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract])	629547
#16	Search (#12 and #15)	**15**
#17	Search “Case-Control Studies”[MeSH] OR “Cohort Studies”[MeSH] OR “Epidemiologic Studies”[MeSH] OR “Follow-Up Studies”[MeSH] OR “Evaluation Studies”[Publication Type] OR “Program Evaluation”[MeSH] OR “observational study”[tw] OR “observational studies”[tw] OR “Cohort Studies”[MeSH] OR “Comparative Study”[pt] OR “Validation Studies”[pt] OR “Prospective Studies”[MeSH] OR “cohort”[tw] OR “case control”[tw]	4116689
#18	Search (#12 and #17)	**282**

Cochrane Library, 8-13-2018

ID	Search	Hits
#1	[mh "Carcinoma, Non-Small-Cell Lung"] or "non-small-cell lung cancer" or NSCLC:ti,ab or ("non small cell":ti,ab and lung*:ti,ab and cancer*:ti,ab) or [mh "Carcinoma, Squamous Cell"] or [mh Adenocarcinoma] or [mh "Carcinoma, Large Cell"]	16679
#2	stag* and (one or "1" or I or two or "2" or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb)	68855
#3	(early or earlier or earliest) and (discover* or found or find or finding or uncover* or diagnos* or detect* or stage* or staging)	52720
#4	#2 or #3	101973
#5	#1 and #4	6519
#6	[mh "Radiosurgery"] OR "stereotactic body radiotherapy" OR SBRT:ti,ab,kw OR "stereotactic body RT" OR "Stereotactic RT" OR "stereotactic ablative radiotherapy" OR SABR:ti,ab,kw	605
#7	#5 and #6	115
#8	letter:pt or newspaper article:pt or editorial:pt or comment:pt	9517
#9	#7 not #8	114
#10	child:ti or child:ab or child:kw or children:ti or children:ab or children:kw or adolescen*:ti or adolescen*:ab or adolescen*:kw or teen:ti or teen:ab or teen:kw or teens:ti or teens:ab or teens:kw or teenage*:ti or teenage*:ab or teenage*:kw or youth:ti or youth:ab or youth:kw or youths:ti or youths:ab or youths:kw or pediatric*:ti or pediatric*:ab or pediatric*:kw or paediatric*:ti or paediatric*:ab or paediatric*:kw or boys:ti or boys:ab or boys:kw or girls:ti or girls:ti or girls:kw	199855
#11	#9 and #10 with Cochrane Library publication date between Jan 2014 and Dec 2018	**3**

Gray Literature

ClinicalTrials.gov, unlimited by status (Completed/Terminated/Has Results, etc.) 5-8-18

Screening

"Other terms" search box:

(screen* OR "Early Diagnosis" OR "X-Ray Computed Tomography" OR "CT scan" OR "CT scans" OR "CAT scan" OR "CAT scans" OR "spiral CT" OR "spiral computed tomography" OR "low-dose computed tomography" OR LDCT OR ((early or earlier or earliest) AND (detect* or diagnos* or discover* or find or finding)) OR DANTE OR "Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays" OR DLCST OR "Danish Lung Cancer Screening Trial" OR ITALUNG OR "Italian Lung Cancer Screening Trial" OR LUSI OR "Lung Cancer Screening Intervention" OR "Multicentric Italian Lung Detection" OR NELSON and Trial* OR "Dutch-Belgian Lung Cancer Screening trial" OR NLST OR "National Lung Screening Trial")

Disease search box

("Lung Neoplasms" OR NSCLC OR "lung cancer" OR "lung cancers" OR "lung-cancer" OR "lung malignancy" OR "lung malignancies" OR "lung nodule" OR "lung nodules" OR "pulmonary nodule" OR "pulmonary nodules" OR "lung mass" OR "lung masses" OR (("Squamous Cell Carcinoma" OR Adenocarcinoma) AND lung*))

Limit to Age Groups Checkboxes for Adult and Senior

Last update posted 01/01/2012–05/08/2018

For a search of:

(screen* OR "Early Diagnosis" OR "X-Ray Computed Tomography" OR "CT scan" OR "CT scans" OR "CAT scan" OR "CAT scans" OR "spiral CT" OR "spiral computed tomography" OR "low-dose computed tomography" OR LDCT OR ((early or earlier or earliest) AND (detect* or diagnos* or discover* or find or finding)) OR DANTE OR "Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays" OR DLCST OR "Danish Lung Cancer Screening Trial" OR ITALUNG OR "Italian Lung Cancer Screening Trial" OR LUSI OR "Lung Cancer Screening Intervention" OR "Multicentric Italian Lung Detection" OR NELSON and Trial* OR "Dutch-Belgian Lung Cancer Screening trial" OR NLST OR "National

Lung Screening Trial") AND ("Lung Neoplasms" OR NSCLC OR "lung cancer" OR "lung cancers" OR "lung-cancer" OR "lung malignancy" OR "lung malignancies" OR "lung nodule" OR "lung nodules" OR "pulmonary nodule" OR "pulmonary nodules" OR "lung mass" OR "lung masses" OR (("Squamous Cell Carcinoma" OR Adenocarcinoma) AND lung*)) [DISEASE] AND INFLECT EXACT ("Adult" OR "Senior") [AGE-GROUP] AND INFLECT ("01/01/2012" : "05/08/2018") [LAST-UPDATE-POSTED]

Intervention search

For a search of:

Condition box:

"Non-Small-Cell Lung Carcinoma" OR "non-small-cell lung cancer" OR NSCLC OR "non small cell" AND lung* AND cancer* OR "Squamous Cell Carcinoma" OR Adenocarcinoma OR "Large Cell Carcinoma"

Other terms box:

(early OR earlier OR earliest) OR (stag* AND (one or 1 or I or two or 2 or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb))

Intervention box:

"Margins of Excision" OR Pneumonectomy OR Lobectomy OR (resection* and lung*) AND INFLECT EXACT ("Adult" OR "Senior") [AGE-GROUP] AND INFLECT ("01/01/2012" : "05/08/2018") [LAST-UPDATE-POSTED]

All together:

early OR (stag* AND (one or 1 or I or two or 2 or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb)) | "Non-Small-Cell Lung Carcinoma" OR "non-small-cell lung cancer" OR NSCLC OR "non small cell" AND lung* AND cancer* OR "Squamous Cell Carcinoma" OR Adenocarcinoma OR "Large Cell Carcinoma" | "Margins of Excision" OR Pneumonectomy OR Lobectomy OR resection* and lung* | Adult, Senior | Last update posted from 01/01/2012 to 05/08/2018

WHO ICTRP 5-4-18

Screening search

Title box:

screen* OR "Early Diagnosis" OR "X-Ray Computed Tomography" OR "CT scan" OR "CT scans" OR "CAT scan" OR "CAT scans" OR "spiral CT" OR "spiral computed tomography" OR "low-dose computed tomography" OR LDCT OR ((early or earlier or earliest) AND (detect* or diagnos* or discover* or find or finding)) OR DANTE OR "Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays" OR DLCST OR "Danish Lung Cancer Screening Trial" OR ITALUNG OR "Italian Lung Cancer Screening Trial" OR LUSI OR "Lung Cancer Screening Intervention" OR "Multicentric Italian Lung Detection" OR (NELSON and Trial*) OR "Dutch-Belgian Lung Cancer Screening trial" OR NLST OR "National Lung Screening Trial"

Condition box:

"Lung Neoplasms" OR NSCLC OR "lung cancer" OR "lung cancers" OR "lung malignancy" OR "lung nodule" OR "lung nodules" OR "pulmonary nodule" OR "pulmonary nodules" OR "lung mass" OR "lung masses" OR "Squamous Cell Carcinoma" OR Adenocarcinoma

Recruitment Status: ALL

Limited to trials registered between Jan 1, 2012 – May 4, 2018

Condition box:

"Lung Neoplasms" OR NSCLC OR "lung cancer" OR "lung cancers" OR "lung malignancy" OR "lung nodule" OR "lung nodules" OR "pulmonary nodule" OR "pulmonary nodules" OR "lung mass" OR "lung masses" OR "Squamous Cell Carcinoma" OR Adenocarcinoma

Intervention search

Condition box:

"Lung Neoplasms" OR NSCLC OR "lung cancer" OR "lung cancers" OR "lung malignancy" OR "lung nodule" OR "lung nodules" OR "pulmonary nodule" OR "pulmonary nodules" OR "lung mass" OR "lung masses" OR "Squamous Cell Carcinoma" OR Adenocarcinoma

Intervention box:

"Margins of Excision" OR Pneumonectomy OR Lobectomy OR (resection* and lung*)

Recruitment Status: ALL

Limited to trials registered between Jan 1, 2012 – May 4, 2018

Gray Literature SBRT Searches

ClinicalTrials.gov, 8-13-2018

For a search of:

Condition box:

"Non-Small-Cell Lung Carcinoma" OR "non-small-cell lung cancer" OR NSCLC OR "non small cell" AND lung* AND cancer* OR "Squamous Cell Carcinoma" OR Adenocarcinoma OR "Large Cell Carcinoma"

Other terms box:

(early OR earlier OR earliest) OR (stag* AND (one or 1 or I or two or 2 or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb))

Intervention box:

Radiosurgery OR "stereotactic body radiotherapy" OR SBRT OR "stereotactic body RT" OR "Stereotactic RT" OR "stereotactic ablative radiotherapy" OR SABR

AND INFLECT EXACT ("Adult" OR "Senior") [AGE-GROUP] AND INFLECT ("01/01/2014" : "08/13/2018") [LAST-UPDATE-POSTED]

WHO ICTRP, 8-14-2018

Condition box:

"Non-Small-Cell Lung Carcinoma" OR "non-small-cell lung cancer" OR NSCLC OR "non small cell" AND lung* AND cancer* OR "Squamous Cell Carcinoma" OR Adenocarcinoma OR "Large Cell Carcinoma"

Intervention box:

Radiosurgery OR "stereotactic body radiotherapy" OR SBRT OR "stereotactic body RT" OR "Stereotactic RT" OR "stereotactic ablative radiotherapy" OR SABR

Recruitment status: ALL

Date of registration between: 01/01/2014 and 08/14/2018

Appendix B1. Original Search Strategies and Update Searches

Update searches
SCREENING
PubMed, May 28, 2019

Search	Query	Items found
#1	Search ("Lung Neoplasms"[MeSH] OR NSCLC[tiab] OR "lung cancer"[tiab] OR "lung cancers" [tiab] OR "lung-cancer"[tiab] OR "lung malignancy"[tiab] OR "lung malignancies"[tiab] OR "lung nodule"[tiab] OR "lung nodules" [tiab] OR "pulmonary nodule"[tiab] OR "pulmonary nodules"[tiab] OR "lung mass"[tiab] OR "lung masses"[tiab] OR ("Squamous Cell Carcinoma"[MeSH] OR Adenocarcinoma[MeSH]) and (Lung[MeSH] OR Lung Diseases[MeSH])))	219968
#2	Search ("Mass Screening"[MeSH] OR screen*[tw] OR "Early Diagnosis"[MeSH] OR "Tomography, X-Ray Computed"[Mesh] OR "CT scan"[tiab] OR "CT scans"[tiab] OR "CAT scan"[tiab] OR "CAT scans"[tiab] OR "spiral CT"[tiab] OR "spiral computed tomography"[tiab] OR "low-dose computed tomography"[tiab] OR LDCT[tiab] OR ((early[tiab] or earlier[tiab] or earliest[tiab]) AND (detect*[tiab] or diagnos*[tiab] or discover*[tiab] or find[tiab] or finding[tiab])))	1677161
#3	Search (#1 and #2)	36110
#4	Search (DANTE[tiab] OR "Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays"[All Fields] OR DLCST[tiab] OR "Danish Lung Cancer Screening Trial"[tiab] OR ITALUNG[tiab] OR "Italian Lung Cancer Screening Trial"[All Fields] OR LUSI[tiab] OR "Lung Cancer Screening Intervention"[All Fields] OR MILD[tiab] OR "Multicentric Italian Lung Detection"[All Fields] OR NELSON[tiab] OR "Dutch-Belgian Lung Cancer Screening trial"[All Fields] OR NLST[tiab] OR "National Lung Screening Trial"[All Fields])	327764
#5	Search (#1 and #4)	2806
#6	Search (#3 or #5)	38027
#7	Search (#3 or #5) Filters: Publication date from 2017/04/30 to 2019/12/31	3454
#8	Search ("Risk prediction model"[tw] OR "Risk prediction models"[tw] OR "Risk Assessment"[MeSH] OR "risk assessment"[tw] OR "risk model"[tw] OR "risk models"[tw] OR "Decision Support Techniques"[MeSH] OR "Decision Support Systems, Clinical"[Mesh] OR "clinical prediction"[tw] OR "Logistic Models"[MeSH] OR microsimulation*[tw] OR "simulation model"[tw] OR "simulation models"[tw] OR "Assessment tool"[tw] OR "Assessment tools"[tw] OR "prediction score"[tw] OR "Risk Factors"[MeSH] OR "Predictive Value of Tests"[MeSH] OR "Sensitivity and Specificity"[MeSH] OR (Predict*[tw] AND (model*[tw] OR outcome*[tw] OR risk*[tw] OR rule[tw] OR rules[tw])) OR "risk-targeted"[tw] OR "mortality risk"[tw])	2231663
#9	Search (#1 and #8)	28279
#10	Search (#1 and #8) Filters: Publication date from 2017/04/30 to 2019/12/31	2628
#11	Search (#7 or #10)	5194
#12	Search (#7 or #10) NOT (animals[mh] NOT humans[mh])	5137
#13	Search (#7 or #10) NOT (animals[mh] NOT humans[mh]) Filters: English	4815
#14	Search (#7 or #10) NOT (animals[mh] NOT humans[mh]) Filters: English; Child: birth-18 years	181
#15	Search ((letter[pt] OR newspaper article[pt] OR editorial[pt] OR comment[pt]))	1744651
#16	Search (#13 not #14)	4634
#17	Search (#16 not #15)	4476
#18	Search ("systematic review"[ti] OR "meta-analysis"[pt] OR "meta-analysis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR ("systematic review"[tiab] AND review[pt]) OR meta synthesis[ti] OR "meta synthesis"[ti] OR "cochrane database syst rev"[ta])	208402
#19	Search (#17 and #18)	**159**
#20	Search "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR ((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract])	656996
#21	Search (#17 and #20)	**118**
#22	Search ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR "Program Evaluation"[MeSH] OR "observational study"[tw] OR "observational studies"[tw] OR "Cohort Studies"[MeSH] OR "Comparative Study"[pt] OR "Validation Studies"[pt] OR "Prospective Studies"[MeSH] OR "cohort"[tw] OR "case control"[tw])	4286922
#23	Search (#17 and #22)	**1908**

Appendix B1. Original Search Strategies and Update Searches

Cochrane Library, May 28, 2019

ID	Cochrane Library Search	Hits
#1	[mh "Lung Neoplasms"] or NSCLC:ti,ab or "lung cancer":ti,ab or "lung cancers":ti,ab or "lung-cancer":ti,ab or "lung malignancy":ti,ab or "lung malignancies":ti,ab or "lung nodule":ti,ab or "lung nodules":ti,ab or "pulmonary nodule":ti,ab or "pulmonary nodules":ti,ab or "lung mass":ti,ab or "lung masses":ti,ab or (([mh "Squamous Cell Carcinoma"] or [mh Adenocarcinoma]) and ([mh Lung] or [mh "Lung Diseases"]))	18607
#2	[mh "Mass Screening"] or screen*:kw or [mh "Early Diagnosis"] or [mh "Tomography, X-Ray Computed"] or "CT scan":ti,ab or "CT scans":ti,ab or "CAT scan":ti,ab or "CAT scans":ti,ab or "spiral CT":ti,ab or "spiral computed tomography":ti,ab or "low-dose computed tomography":ti,ab or LDCT:ti,ab or ((early:ti,ab or earlier:ti,ab or earliest:ti,ab) and (detect*:ti,ab or diagnos*:ti,ab or discover*:ti,ab or find:ti,ab or finding:ti,ab))	51662
#3	#1 and #2	1757
#4	DANTE:ti,ab or "Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays" or DLCST:ti,ab or "Danish Lung Cancer Screening Trial":ti,ab or ITALUNG:ti,ab or "Italian Lung Cancer Screening Trial" or LUSI:ti,ab or "Lung Cancer Screening Intervention" or MILD:ti,ab or "Multicentric Italian Lung Detection" or NELSON:ti,ab or "Dutch-Belgian Lung Cancer Screening trial" or NLST:ti,ab or "National Lung Screening Trial":kw	55900
#5	#1 and #4	643
#6	#3 or #5	2126
#7	#6 Publication Year from April 2017 to 2019	948
#8	"Risk prediction model":ti,ab,kw or "Risk prediction models":ti,ab,kw or [mh "Risk Assessment"] or "risk assessment":ti,ab,kw or "risk model":ti,ab,kw or "risk models":ti,ab,kw or [mh "Decision Support Techniques"] or [mh "Decision Support Systems, Clinical"] or "clinical prediction":ti,ab,kw or [mh "Logistic Models"] or microsimulation*:ti,ab,kw or "simulation model":ti,ab,kw or "simulation models":ti,ab,kw or "Assessment tool":ti,ab,kw or "Assessment tools":ti,ab,kw or "prediction score":ti,ab,kw or [mh "Risk Factors"] or [mh "Predictive Value of Tests"] or [mh "Sensitivity and Specificity"] or (Predict*:ti,ab,kw and (model*:ti,ab,kw or outcome*:ti,ab,kw or risk*:ti,ab,kw or rule:ti,ab,kw or rules:ti,ab,kw)) or "risk-targeted":ti,ab,kw or "mortality risk":ti,ab,kw	114475
#9	#1 and #8	1868
#10	#9 Publication Year from April 2017 to 2019	748
#11	#7 or #10	1514
#12	child:ti or child:ab or child:kw or children:ti or children:ab or children:kw or adolescen*:ti or adolescen*:ab or adolescen*:kw or teen:ti or teen:ab or teen:kw or teens:ti or teens:ab or teens:kw or teenage*:ti or teenage*:ab or teenage*:kw or youth:ti or youth:ab or youth:kw or youths:ti or youths:ab or youths:kw or pediatric*:ti or pediatric*:ab or pediatric*:kw or paediatric*:ti or paediatric*:ab or paediatric*:kw or boys:ti or boys:ab or boys:kw or girls:ti or girls:ti or girls:kw	224306
#13	#11 not #12	1487
#14	#13 in Cochrane Reviews (Reviews and Protocols)	**8**
#15	"randomized controlled trial":pt or "randomized controlled trial":ti or "randomized controlled trial as topic":pt or "single-blind method":pt or "double-blind method":pt or "random allocation":pt	512254
#16	#13 and #15	**160**
#17	[mh "Case-Control Studies"] or [mh "Cohort Studies"] or [mh "Epidemiologic Studies"] or [mh " Follow-Up Studies "] or [mh "Seroepidemiologic Studies"] or "Evaluation Studies":pt or [mh "Program Evaluation"] or "observational study" or "observational studies" or [mh "case-control studies"] or "comparative study":pt or "validation studies":pt or [mh "Prospective Studies"] or "cohort" or "case control"	314610
#18	(#13 and #17) not (#14 or #16) in other study types	**0**

INTERVENTIONS

PubMed, May 28, 2019

Search	Query	Items found
#1	Search ("Carcinoma, Non-Small-Cell Lung"[MeSH] OR "non-small-cell lung cancer"[All Fields] OR NSCLC[tiab] OR ("non small cell"[tiab] AND lung*[tiab] AND cancer*[tiab]) OR "Carcinoma, Squamous Cell"[Mesh] OR Adenocarcinoma[MeSH] OR "Carcinoma, Large Cell"[MeSH])	523587
#2	Search ((stag* AND (one or "1" or I or two or "2" or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb)))	895746
#3	Search ((early or earlier or earliest) AND (discover* or found or find or finding or uncover* or diagnos* or detect* or stage* or staging))	941894

Appendix B1. Original Search Strategies and Update Searches

Search	Query	Items found
#4	Search (#2 or #3)	1601919
#5	Search (#1 and #4)	114508
#6	Search ("Margins of Excision"[Mesh] OR Pneumonectomy OR Lobectomy OR (resection* and lung*[tw]))	40469
#7	Search (#5 and #6)	4291
#8	Search (letter[pt] OR newspaper article[pt] OR editorial[pt] OR comment[pt])	1744651
#9	Search (#7 not #8)	4226
#10	Search (#9 NOT (animals[mh] NOT humans[mh]))	4225
#11	Search (#9 NOT (animals[mh] NOT humans[mh])) Filters: English	3452
#12	Search (#9 NOT (animals[mh] NOT humans[mh])) Filters: Publication date from 2017/05/01 to 2019/12/31; English	536
#13	Search (#9 NOT (animals[mh] NOT humans[mh])) Filters: Publication date from 2017/05/01 to 2019/12/31; English; Child: birth-18 years	18
#14	Search (#12 not #13)	518
#15	Search (("systematic review"[ti] OR "meta-analysis"[pt] OR "meta-analysis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR ("systematic review"[tiab] AND review[pt]) OR meta synthesis[ti] OR "meta synthesis"[ti] OR "cochrane database syst rev"[ta]))	208402
#16	Search (#14 and #15)	**15**
#17	Search ("Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR ((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract]))	656996
#18	Search (#14 and #17)	**13**
#19	Search ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR "Program Evaluation"[MeSH] OR "observational study"[tw] OR "observational studies"[tw] OR "Cohort Studies"[MeSH] OR "Comparative Study"[pt] OR "Validation Studies"[pt] OR "Prospective Studies"[MeSH] OR "cohort"[tw] OR "case control"[tw])	4286922
#20	Search (#14 and #19)	**286**

Appendix B1. Original Search Strategies and Update Searches

Cochrane Library, May 28, 2019

ID	Search	Hits
#1	[mh “Carcinoma, Non-Small-Cell Lung”] or “non-small-cell lung cancer” or NSCLC:ti,ab or (“non small cell”:ti,ab and lung*:ti,ab and cancer*:ti,ab) or [mh “Carcinoma, Squamous Cell”] or [mh Adenocarcinoma] or [mh “Carcinoma, Large Cell”]	20425
#2	stag* and (one or “1” or I or two or “2” or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb)	85688
#3	(early or earlier or earliest) and (discover* or found or find or finding or uncover* or diagnos* or detect* or stage* or staging)	62072
#4	#2 or #3	125155
#5	#1 and #4	8538
#6	([mh “Margins of Excision”] or Pneumonectomy or Lobectomy or (resection* and lung*:ti,ab,kw))	3692
#7	#5 and #6	900
#8	letter:pt or newspaper article:pt or editorial:pt or comment:pt	14366
#9	#7 not #8	897
#10	child:ti or child:ab or child:kw or children:ti or children:ab or children:kw or adolescen*:ti or adolescen*:ab or adolescen*:kw or teen:ti or teen:ab or teen:kw or teens:ti or teens:ab or teens:kw or teenage*:ti or teenage*:ab or teenage*:kw or youth:ti or youth:ab or youth:kw or youths:ti or youths:ab or youths:kw or pediatric*:ti or pediatric*:ab or pediatric*:kw or paediatric*:ti or paediatric*:ab or paediatric*:kw or boys:ti or boys:ab or boys:kw or girls:ti or girls:ti or girls:kw	224306
#11	#9 not #10	880
#12	#11 Publication Year from 2017 to 2019, in Cochrane Reviews, Cochrane Protocols	**9**
#13	“randomized controlled trial”:pt or “randomized controlled trial”:ti or “randomized controlled trial as topic”:pt or “single-blind method”:pt or “double-blind method”:pt or “random allocation”:pt	512254
#14	#11 and #13 Publication Year from 2017 to 2019, in Trials	**30**
#15	[mh “Case-Control Studies”] or [mh “Cohort Studies”] or [mh “Epidemiologic Studies”] or [mh “ Follow-Up Studies “] or [mh “Seroepidemiologic Studies”] or “Evaluation Studies”:pt or [mh “Program Evaluation”] or “observational study” or “observational studies” or [mh “case-control studies”] or “comparative study”:pt or “validation studies”:pt or [mh “Prospective Studies”] or “cohort” or “case control”	314610
#16	#11 and #15 publication date from May 2017 to Dec 2019, in Clinical Answers and Special collections	**0**

SBRT-SABR SEARCHES

PubMed, 5-28-19

Search	Query	Items found
#1	Search ((“Carcinoma, Non-Small-Cell Lung”[MeSH] OR “non-small-cell lung cancer”[All Fields] OR NSCLC[tiab] OR (“non small cell”[tiab] AND lung*[tiab] AND cancer*[tiab]) OR “Carcinoma, Squamous Cell”[Mesh] OR Adenocarcinoma[MeSH] OR “Carcinoma, Large Cell”[MeSH]))	523587
#2	Search (stag* AND (one or “1” or I or two or “2” or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb))	895746
#3	Search ((early or earlier or earliest) AND (discover* or found or find or finding or uncover* or diagnos* or detect* or stage* or staging))	941894
#4	Search (#2 or #3)	1601919
#5	Search (#1 and #4)	114508
#6	Search (“Radiosurgery”[Mesh] OR “stereotactic body radiotherapy” OR SBRT[tw] OR “stereotactic body RT” OR “Stereotactic RT” OR “stereotactic ablative radiotherapy” OR SABR[tw])	15921
#7	Search ((#5 and #6))	1217
#8	Search (letter[pt] OR newspaper article[pt] OR editorial[pt] OR comment[pt])	1744651
#9	Search (#7 not #8)	1176
#10	Search (#9 NOT (animals[mh] NOT humans[mh]))	1174
#11	Search (#9 NOT (animals[mh] NOT humans[mh])) Filters: English	1117
#12	Search (#9 NOT (animals[mh] NOT humans[mh])) Filters: Publication date from 2017/08/10 to 2019/12/31; English	253
#13	Search (((“systematic review”[ti] OR “meta-analysis”[pt] OR “meta-analysis”[ti] OR “systematic literature review”[ti] OR “this systematic review”[tw] OR (“systematic review”[tiab] AND review[pt]) OR meta synthesis[ti] OR “meta synthesis”[ti] OR “cochrane database syst rev”[ta]))	208402
#14	Search (#12 and #13)	**7**
#15	Search (“Randomized Controlled Trial”[Publication Type] OR “Single-Blind Method”[MeSH] OR “Double-Blind Method”[MeSH] OR “Random Allocation”[MeSH] OR ((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract]))	656996
#16	Search (#12 and #15)	**5**
#17	Search (“Case-Control Studies”[MeSH] OR “Cohort Studies”[MeSH] OR “Epidemiologic Studies”[MeSH] OR “Follow-Up Studies”[MeSH] OR “Evaluation Studies”[Publication Type] OR “Program Evaluation”[MeSH] OR “observational study”[tw] OR “observational studies”[tw] OR “Cohort Studies”[MeSH] OR “Comparative Study”[pt] OR “Validation Studies”[pt] OR “Prospective Studies”[MeSH] OR “cohort”[tw] OR “case control”[tw])	4286922
#18	Search (#12 and #17)	**108**

Cochrane Library, 5-28-19, SABR search

ID	Search	Hits
#1	[mh "Carcinoma, Non-Small-Cell Lung"] or "non-small-cell lung cancer" or NSCLC:ti,ab or ("non small cell":ti,ab and lung*:ti,ab and cancer*:ti,ab) or [mh "Carcinoma, Squamous Cell"] or [mh Adenocarcinoma] or [mh "Carcinoma, Large Cell"]	20425
#2	stag* and (one or "1" or I or two or "2" or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb)	85688
#3	(early or earlier or earliest) and (discover* or found or find or finding or uncover* or diagnos* or detect* or stage* or staging)	62072
#4	#2 or #3	125155
#5	#1 and #4	8538
#6	[mh "Radiosurgery"] OR "stereotactic body radiotherapy" OR SBRT:ti,ab,kw OR "stereotactic body RT" OR "Stereotactic RT" OR "stereotactic ablative radiotherapy" OR SABR:ti,ab,kw	779
#7	#5 and #6	170
#8	letter:pt or newspaper article:pt or editorial:pt or comment:pt	14366
#9	#7 not #8	169
#10	child:ti or child:ab or child:kw or children:ti or children:ab or children:kw or adolescen*:ti or adolescen*:ab or adolescen*:kw or teen:ti or teen:ab or teen:kw or teens:ti or teens:ab or teens:kw or teenage*:ti or teenage*:ab or teenage*:kw or youth:ti or youth:ab or youth:kw or youths:ti or youths:ab or youths:kw or pediatric*:ti or pediatric*:ab or pediatric*:kw or paediatric*:ti or paediatric*:ab or paediatric*:kw or boys:ti or boys:ab or boys:kw or girls:ti or girls:ti or girls:kw	224306
#11	#9 not #10 with Cochrane Library publication date from Jan 2014 to Dec 2019	163
#12	#11 in in Cochrane Reviews and Cochrane Protocols	**4**
#13	"randomized controlled trial":pt or "randomized controlled trial":ti or "randomized controlled trial as topic":pt or "single-blind method":pt or "double-blind method":pt or "random allocation":pt	512254
#14	#11 and #13	**17**
#15	[mh "Case-Control Studies"] or [mh "Cohort Studies"] or [mh "Epidemiologic Studies"] or [mh " Follow-Up Studies "] or [mh "Seroepidemiologic Studies"] or "Evaluation Studies":pt or [mh "Program Evaluation"] or "observational study" or "observational studies" or [mh "case-control studies"] or "comparative study":pt or "validation studies":pt or [mh "Prospective Studies"] or "cohort" or "case control"	314610
#16	(#11 and #15) NOT (#12 or #14) in Cochrane Reviews, Cochrane Protocols, Trials, Clinical Answers and Special collections	**19**

Lung Cancer Gray Literature Updates, May 28, 2019

SCREENING

ClinicalTrials.gov, May 28, 2019

436 results

"Other terms" search box**:**

(screen* OR "Early Diagnosis" OR "X-Ray Computed Tomography" OR "CT scan" OR "CT scans" OR "CAT scan" OR "CAT scans" OR "spiral CT" OR "spiral computed tomography" OR "low-dose computed tomography" OR LDCT OR ((early or earlier or earliest) AND (detect* or diagnos* or discover* or find or finding)) OR DANTE OR "Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays" OR DLCST OR "Danish Lung Cancer Screening Trial" OR ITALUNG OR "Italian Lung Cancer Screening Trial" OR LUSI OR "Lung Cancer Screening Intervention" OR "Multicentric Italian Lung Detection" OR NELSON and Trial* OR "Dutch-Belgian Lung Cancer Screening trial" OR NLST OR "National Lung Screening Trial")

Disease search box:

("Lung Neoplasms" OR NSCLC OR "lung cancer" OR "lung cancers" OR "lung-cancer" OR "lung malignancy" OR "lung malignancies" OR "lung nodule" OR "lung nodules" OR "pulmonary nodule" OR "pulmonary nodules" OR "lung mass" OR "lung masses" OR (("Squamous Cell Carcinoma" OR Adenocarcinoma) AND lung*))

Limit to age groups checkboxes for Adult and Older Adults

Last update posted 05/01/2018 – 05/28/2018

WHO ICTRP, May 28, 2019
51 results
Title box:
screen* OR "Early Diagnosis" OR "X-Ray Computed Tomography" OR "CT scan" OR "CT scans" OR "CAT scan" OR "CAT scans" OR "spiral CT" OR "spiral computed tomography" OR "low-dose computed tomography" OR LDCT OR ((early or earlier or earliest) AND (detect* or diagnos* or discover* or find or finding)) OR DANTE OR "Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays" OR DLCST OR "Danish Lung Cancer Screening Trial" OR ITALUNG OR "Italian Lung Cancer Screening Trial" OR LUSI OR "Lung Cancer Screening Intervention" OR "Multicentric Italian Lung Detection" OR (NELSON and Trial*) OR "Dutch-Belgian Lung Cancer Screening trial" OR NLST OR "National Lung Screening Trial"
Condition box:
"Lung Neoplasms" OR NSCLC OR "lung cancer" OR "lung cancers" OR "lung malignancy" OR "lung nodule" OR "lung nodules" OR "pulmonary nodule" OR "pulmonary nodules" OR "lung mass" OR "lung masses" OR "Squamous Cell Carcinoma" OR Adenocarcinoma
Recruitment Status: ALL
Limited to trials registered between May 1, 2018 – May 28, 2019

INTERVENTIONS
ClinicalTrials.gov, May 28, 2019
40 results
Condition box:
"Non-Small-Cell Lung Carcinoma" OR "non-small-cell lung cancer" OR NSCLC OR "non small cell" AND lung* AND cancer* OR "Squamous Cell Carcinoma" OR Adenocarcinoma OR "Large Cell Carcinoma"
Other terms box:
(early OR earlier OR earliest) OR (stag* AND (one or 1 or I or two or 2 or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb))
Intervention box:
"Margins of Excision" OR Pneumonectomy OR Lobectomy OR (resection* and lung*)
Limit to age groups checkboxes for Adult and Older Adult
Last update posted 05/01/2018 – 05/28/2019
WHO ICTRP, May 28, 2019
26 results
Condition box:
"Lung Neoplasms" OR NSCLC OR "lung cancer" OR "lung cancers" OR "lung malignancy" OR "lung nodule" OR "lung nodules" OR "pulmonary nodule" OR "pulmonary nodules" OR "lung mass" OR "lung masses" OR "Squamous Cell Carcinoma" OR Adenocarcinoma
Intervention box:
"Margins of Excision" OR Pneumonectomy OR Lobectomy OR (resection* and lung*)
Recruitment Status: ALL
Limited to trials registered between May 1, 2018 – May 28, 2019

SBRT-SABR
ClinicalTrials.gov, May 28, 2019
55 results

Condition box
"Non-Small-Cell Lung Carcinoma" OR "non-small-cell lung cancer" OR NSCLC OR "non small cell" AND lung* AND cancer* OR "Squamous Cell Carcinoma" OR Adenocarcinoma OR "Large Cell Carcinoma"
Other terms box:
(early OR earlier OR earliest) OR (stag* AND (one or 1 or I or two or 2 or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb))
Intervention box:
Radiosurgery OR "stereotactic body radiotherapy" OR SBRT OR "stereotactic body RT" OR "Stereotactic RT" OR "stereotactic ablative radiotherapy" OR SABR
Limit to age groups checkboxes for Adult and Older Adults
Last update posted 05/01/2018 – 05/28/2018
WHO ICTRP, May 28, 2019
87 results
Condition box:
"Non-Small-Cell Lung Carcinoma" OR "non-small-cell lung cancer" OR NSCLC OR "non small cell" AND lung* AND cancer* OR "Squamous Cell Carcinoma" OR Adenocarcinoma OR "Large Cell Carcinoma"
Intervention box:
Radiosurgery OR "stereotactic body radiotherapy" OR SBRT OR "stereotactic body RT" OR "Stereotactic RT" OR "stereotactic ablative radiotherapy" OR SABR
Recruitment status: ALL
Date of registration between: 05/01/2018 – 05/28/2018

Appendix B2. Eligibility Criteria

	Include	Exclude
Populations	**KQs 1–5, 8:** Asymptomatic adults (age ≥18 years) **KQs 6, 7:** Adults (age ≥18 years) with early (Stage I) non-small cell lung cancer	**KQs 1–5, 8:** Children, persons with symptoms or prior diagnosis of lung cancer **KQs 6, 7**: Children, persons with nonprimary lung cancer or other than Stage I lung cancer
Risk prediction	**KQ 2:** Externally validated models including demographic variables, clinical variables, or biomarkers intended for identifying persons at increased risk who are more likely to benefit from screening	**KQ 2:** Models including a single variable or biomarker, models not considering smoking and age (known risk factors for lung cancer)
Screening	**KQs 1, 3, 4, 8:** LDCT*	**KQs 1, 3, 4, 8:** No screening, chest X-ray, sputum cytology, and other screening modalities
Workup or surveillance	**KQ 5:** Computed tomography, biopsy, positron emission tomography, or other tests used after screening	Not applicable
Interventions	**KQs 6, 7:** Surgical resection or SBRT	**KQs 6, 7:** Chemotherapy, natural therapies, immunotherapy, or targeted molecular therapy
Comparisons	**KQs 1, 8:** Chest X-ray, no screening, or usual care **KQ 2:** 2013 USPSTF recommendations or criteria used by trials showing benefit (e.g., NLST) **KQ 3:** • There is no single gold standard for assessing accuracy • Comparison (reference standard) could be subsequent diagnosis of lung cancer within 1 year (likely resulting from repeat imaging and subsequent biopsy), biopsy, or subsequent imaging • Sensitivity and false-negative screens (false reassurance): Typically determined by considering new lung cancer presenting within 1 year of a normal screening study as false-negative screens • Specificity and false-positive screens: Initial positive LDCT result that is found to be benign with tissue diagnosis or subsequent imaging **KQs 4, 5:** Chest X-ray, no screening, usual care, or no comparison group **KQs 6, 7:** No comparison group is required; although the review did not assess comparative effectiveness of treatments, comparative effectiveness studies were eligible if they provided data for eligible populations, interventions, and outcomes and met the other eligibility criteria	**KQs 1–3, 8:** Studies without a comparison group

Appendix B2. Eligibility Criteria

	Include	Exclude
Outcomes	**KQ 1a:** Incidence of lung cancer (all stages), distribution of lung cancer types and stages **KQ 1b:** All-cause mortality, lung cancer mortality, quality of life, or functional status **KQ 2:** Estimated number of deaths from lung cancer or all-cause mortality that can be prevented by screening, estimated screening effectiveness (e.g., number needed to screen), or estimated screening harms **KQ 3:** Sensitivity, specificity, and predictive value **KQ 4:** Radiation exposure, false-positive results, overdiagnosis,† smoking cessation rates, psychosocial harms, incidental findings leading to additional tests and subsequent harms, and unnecessary treatment (e.g., surgical resection for a benign nodule) **KQ 5**: Radiation exposure, false-positive results, overdiagnosis,† smoking cessation rates, psychosocial harms, incidental findings leading to additional tests and subsequent harms, unnecessary treatment (e.g., surgical resection for a benign nodule), and harms of workup (e.g., biopsy leading to an adverse event) **KQ 6:** 5- and 10-year incidence of advanced disease and mortality (survival rates) **KQ 7:** Harms of treatment, including mortality, infection, bleeding, bronchopleural fistula, and respiratory failure **KQ 8:** All-cause and lung cancer mortality	Costs
Study designs	All KQs: Controlled trials **KQ 2:** Modeling studies are also eligible, clinical prediction tools must include multiple factors **KQ 3:** Studies evaluating accuracy are also eligible **KQs 4, 5, 7:** Prospective cohort and case-control studies are also eligible **KQ 6:** Prospective cohort studies are also eligible	All other study designs‡ **KQ 2:** Models including a single variable or biomarker, models not considering smoking and age (known risk factors for lung cancer) **KQs 1–5, 8:** Studies with a sample size less than 1,000 **KQs 6, 7:** For surgery (established standard treatment), studies with a sample size less than 500; for SBRT, no limit on sample size
Study duration	**KQs 1–5, 7, 8:** Any length of time **KQ 6:** At least 5 years of followup	**KQ 6:** Less than 5 years of followup
Settings	Published in or after 2001	
Countries	Studies conducted in countries categorized as “Very High” on the 2016 Human Development Index (as defined by the United Nations Development Programme)	Studies conducted in countries that are not categorized as “Very High” on the 2016 Human Development Index
Language	English	Languages other than English
Study quality	Good or fair quality	Poor quality (according to design-specific USPSTF criteria)

* The review focused on computed tomography but also searched for and allowed for inclusion of new trials (published since the search cutoff dates of the last review) of other screening modalities. Older studies (before 2013) of other screening modalities were not carried forward to this update.

† Defined as detection of disease that would never progress to produce symptoms or death.

‡ Systematic reviews are excluded from the evidence review. However, separate searches were conducted to identify relevant systematic reviews, and the citations of all studies included in those systematic reviews were reviewed to ensure that database searches captured all relevant primary studies.

Abbreviations: KQ=key question; LDCT=low-dose computed tomography; NLST=National Lung Screening Trial; SBRT=stereotactic body radiotherapy; USPSTF=U.S. Preventive Services Task Force.

Randomized, Controlled Trials and Cohort Studies

Criteria

- Initial assembly of comparable groups
- Randomized, controlled trials (RCTs)—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements that are equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria

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

Fair: Studies will be graded "fair" if any or all of the following problems occur without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and 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 is lacking for RCTs.

Poor: Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Sources: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2015[51]

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of Ratings Based on Above Criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (greater than 100) of broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has a fatal flaw, such as uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2015[51]

Appendix C. Excluded Studies

X1. Non-English
X2. Abstract only
X3. Ineligible population
X4. Ineligible risk prediction model
X5. Ineligible screening modality
X6. Ineligible intervention
X7. Ineligible comparator
X8. Ineligible outcome(s)
X9. Ineligible study design
X10. Ineligible study design
X11. Ineligible sample size
X12. Ineligible duration for KQ 6 (surgery studies)
X13. Ineligible duration for KQ 6 (SBRT/SABR studies)
X14. Eligible, except for country setting
X15. Eligible, except published prior to 2001
X16. Irretrievable
X17. Poor quality

1. How big is too big for lung nodules on screening scans? *BMJ*. 2013 Feb 20;346:f1070. doi: 10.1136/bmj.f1070. PMID: 23427128. E[73]xclusion Code: X2.
2. Who to screen for lung cancer. *BMJ*. 2013 Jul 23;347:f4686. doi: 10.1136/bmj.f4686. PMID: 23882010. Exclusion Code: X10.
3. Quality of life following stereotactic ablative radiation therapy versus surgery for early-stage lung cancer: results from the rosel randomized controlled trial and a systematic review. *International journal of radiation oncology*. 2016;Conference: 58th Annual Meeting of the American Society for Radiation Oncology, ASTRO 2016. United States. 96(2 Supplement 1):S10-S1. doi: 10.1016/j.ijrobp.2016.06.039. PMID: CN-01448175. Exclusion Code: X2.
4. Abdelsattar ZM, Allen MS, Shen KR, et al. Variation in hospital adoption rates of video-assisted thoracoscopic lobectomy for lung cancer and the effect on outcomes. *Ann Thorac Surg*. 2017 Feb;103(2):454-60. doi: 10.1016/j.athoracsur.2016.08.091. PMID: 27825690. Exclusion Code: X3.
5. Abdelsattar ZM, Shen KR, Yendamuri S, et al. Outcomes after sleeve lung resections versus pneumonectomy in the United States. *Ann Thorac Surg*. 2017 Nov;104(5):1656-64. doi: 10.1016/j.athoracsur.2017.05.086. PMID: 28935348. Exclusion Code: X3.
6. Abdul Rahim M, North J, Costello S. Stereotactic ablative radiotherapy for inoperable early stage non-small cell lung cancer-Dunedin experience. *J Med Imaging Radiat Oncol*. 2013;57:120-. doi: 10.1111/1754-9485.12121. PMID: CN-01011012. Exclusion Code: X2.
7. Abdulla S, Salavati A, Saboury B, et al. Quantitative assessment of global lung inflammation following radiation therapy using FDG PET/CT: a pilot study. *Eur J Nucl Med Mol Imaging*. 2014 Feb;41(2):350-6. doi: 10.1007/s00259-013-2579-4. PMID: 24085504. Exclusion Code: X3.
8. Abe J, Okazaki T, Kikuchi N, et al. Preoperative bronchoscopic cancer confirmation does not increase risk of recurrence in stage1A non-small cell lung cancer. *Gen Thorac Cardiovasc Surg*. 2018 May;66(5):284-90. doi: 10.1007/s11748-018-0909-y. PMID: 29564776. Exclusion Code: X8.
9. Abe T, Shirai K, Saitoh J, et al. Incidence, risk factors, and dose-volume relationship of radiation-induced rib fracture after carbon ion radiotherapy for lung cancer. *Acta Oncol*. 2016;55(2):163-6. doi: 10.3109/0284186x.2015.1088169. PMID: 26399488. Exclusion Code: X6.

10. Aberle DR, Adams AM, Berg CD, et al. Baseline characteristics of participants in the randomized national lung screening trial. *J Natl Cancer Inst*. 2010 Dec 1;102(23):1771-9. doi: 10.1093/jnci/djq434. PMID: 21119104. Exclusion Code: X8.
11. Abramyuk A, Appold S, Zophel K, et al. Quantitative modifications of TNM staging, clinical staging and therapeutic intent by FDG-PET/CT in patients with non small cell lung cancer scheduled for radiotherapy--a retrospective study. *Lung Cancer*. 2012 Nov;78(2):148-52. doi: 10.1016/j.lungcan.2012.08.001. PMID: 22922126. Exclusion Code: X3.
12. Accordino MK, Wright JD, Buono D, et al. Trends in use and safety of image-guided transthoracic needle biopsies in patients with cancer. *J Oncol Pract*. 2015 May;11(3):e351-9. doi: 10.1200/jop.2014.001891. PMID: 25604594. Exclusion Code: X3.
13. Adebahr S, Collette S, Shash E, et al. LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective. *Br J Radiol*. 2015 Jul;88(1051):20150036. doi: 10.1259/bjr.20150036. PMID: 25873481. Exclusion Code: X10.
14. Advani M, Purohit G, Vyas S, et al. Comparison of Diagnostic Potential of Narrow Band Imaging Bronchoscopy Over White Light Bronchoscopy in Lung Cancer. *J Bronchology Interv Pulmonol*. 2018 Apr;25(2):132-6. doi: 10.1097/lbr.0000000000000469. PMID: 29346246. Exclusion Code: X3.
15. Agostini P, Lugg ST, Adams K, et al. Postoperative pulmonary complications and rehabilitation requirements following lobectomy: a propensity score matched study of patients undergoing video-assisted thoracoscopic surgery versus thoracotomydagger. *Interact Cardiovasc Thorac Surg*. 2017 Jun 1;24(6):931-7. doi: 10.1093/icvts/ivx002. PMID: 28329213. Exclusion Code: X3.
16. Agostini PJ, Lugg ST, Adams K, et al. Risk factors and short-term outcomes of postoperative pulmonary complications after VATS lobectomy. *J Cardiothorac Surg*. 2018 Apr 12;13(1):28. doi: 10.1186/s13019-018-0717-6. PMID: 29673386. Exclusion Code: X11.
17. Agzarian J, Hanna WC, Schneider L, et al. Postdischarge venous thromboembolic complications following pulmonary oncologic resection: An underdetected problem. *J Thorac Cardiovasc Surg*. 2016 Apr;151(4):992-9. doi: 10.1016/j.jtcvs.2015.11.038. PMID: 26707765. Exclusion Code: X3.
18. Ahmed N, Hasan S, Schumacher L, et al. Stereotactic body radiotherapy for central lung tumors: Finding the balance between safety and efficacy in the "no fly" zone. *Thorac Cancer*. 2018 Oct;9(10):1211-4. doi: 10.1111/1759-7714.12764. PMID: 30095228. Exclusion Code: X3.
19. Ahn H, Lee KW, Lee KH, et al. Effect of computed tomography window settings and reconstruction plane on 8th edition T-stage classification in patients with lung adenocarcinoma manifesting as a subsolid nodule. *Eur J Radiol*. 2018 Jan;98:130-5. doi: 10.1016/j.ejrad.2017.11.015. PMID: 29279151. Exclusion Code: X3.
20. Ahn SY, Yoon SH, Yang BR, et al. Risk of pleural recurrence after percutaneous transthoracic needle biopsy in stage I non-small-cell lung cancer. *Eur Radiol*. 2019 Jan;29(1):270-8. doi: 10.1007/s00330-018-5561-5. PMID: 29948086. Exclusion Code: X11.
21. Ai D, Xu G, Feng L, et al. Dexmedetomidine does not reduce atrial fibrillation after lung cancer surgery. *J Cardiothorac Vasc Anesth*. 2015 Apr;29(2):396-401. doi: 10.1053/j.jvca.2014.05.013. PMID: 25440618. Exclusion Code: X3.
22. Akashita S, Tachibana Y, Sakamaki K, et al. Detection of pure ground-glass nodules in the lung by low-dose multi-detector computed tomography, with use of an iterative reconstruction method: a comparison with conventional image reconstruction by the filtered back-projection method. *Jpn J Radiol*. 2015 Mar;33(3):113-21. doi: 10.1007/s11604-014-0384-z. PMID: 25552203. Exclusion Code: X3.
23. Akin H, Olcmen A, Isgorucu O, et al. Approach to patients with chylothorax complicating pulmonary resection. *Thorac Cardiovasc Surg*. 2012 Mar;60(2):135-9. doi: 10.1055/s-0030-1270990. PMID: 21557161. Exclusion Code: X3.

24. Akthar AS, Ferguson MK, Koshy M, et al. Limitations of PET/CT in the detection of occult N1 metastasis in clinical stage I(T1-2aN0) non-small cell lung cancer for staging prior to stereotactic body radiotherapy. *Technol Cancer Res Treat*. 2017 Feb;16(1):15-21. doi: 10.1177/1533034615624045. PMID: 26792491. Exclusion Code: X6.
25. Akthar AS, Koshy M, Ferguson MK, et al. Effect of endoscopic bronchial ultrasound on outcomes for stage i non-small-cell lung cancer patients receiving hypofractionated radiotherapy. *Clin Lung Cancer*. 2018 Mar;19(2):e227-e33. doi: 10.1016/j.cllc.2017.08.003. PMID: 28939097. Exclusion Code: X10.
26. Al-Alao BS, O'Callaghan DS, Gately K, et al. Surgical resection for non-small cell lung cancer: clinical features and outcomes for a consecutive series at an Irish tertiary referral centre. *Ir J Med Sci*. 2013 Jun;182(2):217-25. doi: 10.1007/s11845-012-0863-0. PMID: 23139062. Exclusion Code: X11.
27. Al-Ameri A, Malhotra P, Thygesen H, et al. Risk of malignancy in pulmonary nodules: a validation study of four prediction models. *Lung Cancer*. 2015 Jul;89(1):27-30. doi: 10.1016/j.lungcan.2015.03.018. PMID: 25864782. Exclusion Code: X4.
28. Al-Ameri M, Bergman P, Franco-Cereceda A, et al. Video-assisted thoracoscopic versus open thoracotomy lobectomy: a Swedish nationwide cohort study. *J Thorac Dis*. 2018 Jun;10(6):3499-506. doi: 10.21037/jtd.2018.05.177. PMID: 30069346. Exclusion Code: X3.
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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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1936. Yuan X, Zhang J, Quan C, et al. Differentiation of malignant and benign pulmonary nodules with first-pass dual-input perfusion CT. *Eur Radiol*. 2013 Sep;23(9):2469-74. doi: 10.1007/s00330-013-2842-x. PMID: 23793548. Exclusion Code: X3.

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1945. Zhang B, Lee SW, Chen S, et al. Action Levels on Dose and Anatomic Variation for Adaptive Radiation Therapy Using Daily Offline Plan Evaluation: Preliminary Results. *Pract Radiat Oncol*. 2019 Jan;9(1):49-54. doi: 10.1016/j.prro.2018.08.006. PMID: 30142442. Exclusion Code: X6.

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Appendix C. Excluded Studies

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1948. Zhang G, Zou L, Xu H. Anodic alumina coating for extraction of volatile organic compounds in human exhaled breath vapor. *Talanta*. 2015 Jan;132:528-34. doi: 10.1016/j.talanta.2014.09.035. PMID: 25476340. Exclusion Code: X5.

1949. Zhang H, Gao S, Chen B, et al. Comparison of the accuracy of ^{99m}Tc-3P<inf>4</inf>-RGD<inf>2</inf> SPECT and CT in diagnosing solitary pulmonary nodules. *Oncol Lett*. 2016;12(4):2517-23. doi: 10.3892/ol.2016.5030. PMID: CN-01211975. Exclusion Code: X3.

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1968. Zhao L, Tong L, Lin J, et al. Characterization of solitary pulmonary nodules with 18F-FDG PET/CT relative activity distribution analysis. *Eur Radiol*. 2015 Jul;25(7):1837-44. doi: 10.1007/s00330-015-3592-8. PMID: 25636419. Exclusion Code: X3.

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1972. Zhao Y, de Bock GH, Vliegenthart R, et al. Performance of computer-aided detection of pulmonary nodules in low-dose CT: comparison with double reading by nodule volume. *Eur Radiol*. 2012 Oct;22(10):2076-84. doi: 10.1007/s00330-012-2437-y. PMID: 22814824. Exclusion Code: X11.

1973. Zhao ZR, Xi SY, Li W, et al. Prognostic impact of pattern-based grading system by the new IASLC/ATS/ERS classification in Asian patients with stage I lung adenocarcinoma. *Lung Cancer*. 2015 Dec;90(3):604-9. doi: 10.1016/j.lungcan.2015.10.026. PMID: 26547801. Exclusion Code: X11.

1974. Zheng A, Wang X, Yang X, et al. Major complications after lung microwave ablation: a single-center experience on 204 sessions. *Ann Thorac Surg*. 2014 Jul;98(1):243-8. doi: 10.1016/j.athoracsur.2014.03.008. PMID: 24793688. Exclusion Code: X6.

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1977. Zheng X, Xiong H, Li Y, et al. Application of quantitative autofluorescence bronchoscopy image analysis method in identifying bronchopulmonary cancer. *Technol Cancer Res Treat*. 2017 Aug;16(4):482-7. doi: 10.1177/1533034616656466. PMID: 27436838. Exclusion Code: X3.
1978. Zheng Y, Shi A, Wang W, et al. Posttreatment Immune Parameters Predict Cancer Control and Pneumonitis in Stage I Non-Small-Cell Lung Cancer Patients Treated With Stereotactic Ablative Radiotherapy. *Clin Lung Cancer*. 2018 Jul;19(4):e399-e404. doi: 10.1016/j.cllc.2017.12.012. PMID: 29519614. Exclusion Code: X10.
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1980. Zhong C, Yao F, Zhao H. Clinical outcomes of thoracoscopic lobectomy for patients with clinical N0 and pathologic N2 non-small cell lung cancer. *Ann Thorac Surg*. 2013 Mar;95(3):987-92. doi: 10.1016/j.athoracsur.2012.10.083. PMID: 23261117. Exclusion Code: X3.
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1982. Zhou H, Tapias LF, Gaissert HA, et al. Lymph node assessment and impact on survival in video-assisted thoracoscopic lobectomy or segmentectomy. *Ann Thorac Surg*. 2015 Sep;100(3):910-6. doi: 10.1016/j.athoracsur.2015.04.034. PMID: 26165483. Exclusion Code: X17.
1983. Zhou S, Pei G, Han Y, et al. Sleeve lobectomy by video-assisted thoracic surgery versus thoracotomy for non-small cell lung cancer. *J Cardiothorac Surg*. 2015 Sep 10;10:116. doi: 10.1186/s13019-015-0318-6. PMID: 26357875. Exclusion Code: X3.
1984. Zhou T, Lu H, Zhang J, et al. Pulmonary nodule detection model based on SVM and CT image feature-level fusion with rough sets. *Biomed Res Int*. 2016;2016:8052436. doi: 10.1155/2016/8052436. PMID: 27722173. Exclusion Code: X3.
1985. Zhu H, Zhang L, Wang Y, et al. Improved image quality and diagnostic potential using ultra-high-resolution computed tomography of the lung with small scan FOV: A prospective study. *PLoS One*. 2017;12(2):e0172688. doi: 10.1371/journal.pone.0172688. PMID: 28231320. Exclusion Code: X3.
1986. Zhu J, Zhang HP, Ni J, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for diagnosing mediastinal lymphadenectasis: a cohort study from a single center. *Clin Respir J*. 2017 Mar;11(2):159-67. doi: 10.1111/crj.12317. PMID: 25918974. Exclusion Code: X3.
1987. Zhuang YP, Wang HY, Zhang J, et al. Diagnostic accuracy and safety of CT-guided fine needle aspiration biopsy in cavitary pulmonary lesions. *Eur J Radiol*. 2013 Jan;82(1):182-6. doi: 10.1016/j.ejrad.2012.09.011. PMID: 23079048. Exclusion Code: X3.
1988. Zimmermann M, Nickl S, Lambers C, et al. Discrimination of clinical stages in non-small cell lung cancer patients by serum HSP27 and HSP70: a multi-institutional case-control study. *Clin Chim Acta*. 2012 Jul 11;413(13-14):1115-20. doi: 10.1016/j.cca.2012.03.008. PMID: 22465083. Exclusion Code: X7.
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Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Ackerson, 2018[295] N/A Fair	NA	Medium	Low	Low	NI	Medium	Low	Nearly a quarter (24%) of SBRT patients lacked pathologic confirmation of NSCLC; ROB stemming from this small study with some data collected retrospectively (70 SBRT patients).
Allibhai, 2013[259] NA Fair	NA	Low	Low	NI	NI	Low	High	There was no information on deviations from the intended SBRT therapy or on missing data reported in the article. Additionally, the only adverse event reported was radiation pneumonitis.
Anderson, 2009[150] ELCAP Fair	NA	Medium	Low	Low	Low	Medium	Low	Risk of selection bias and self-reported outcome
Arnold, 2017[199] NCDB: 2003-2012 Fair	NA	Medium	Low	NI	Low	Low	Low	Risk of selection bias, as reported by the authors, and lack of information on deviations from treatment before entry into the study.
Badellino, 2017[270] NA Fair	NA	Low	Low	Low	NI	Medium	Medium	Risk for information and reporting bias related to the outcomes and no information on missing data.
Baine, 2019[232] NCDB: 2004-2014 Fair	NA	Low	Low	NI	Low	Medium	Low	Risk of outcome measurement bias; lack of detail about systems for outcome ascertainment.
Ball, 2019[293] CHISEL Fair	NA	Medium	Low	Low	Low	Low	Medium	Risk of selection bias because nearly half (43%) of the SBRT sample had a history of previous cancer, and also risk of reporting bias because the trial protocol did not require the recording of toxicities occurring after local treatment failure

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First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Barriger, 2012[290] N/A Fair	NA	Medium	Medium	NI	Medium	Medium	Low	Risk of selection bias; unclear how many patients had histologically confirmed NSCLC; ROB due to intervention classification because different treatment planning systems were used depending on the year of treatment; potential missing data bias because of the exclusion of patients with incomplete dosimetry data.
Baumann, 2006[227] N/A Fair	NA	Low	Low	NI	Low	Medium	Low	Risk of outcome measurement bias because of ascertainment methods used.
Berry, 2018[216] California Cancer Registry: 2013-2014 Fair	NA	Medium	Low	NI	Low	Low	Low	Risk of selection bias; no detail was given about how patients' cancers were staged; no information about potential deviation from intended surgeries.
Bibault, 2015[254] NA Fair	NA	Medium	Low	NI	NI	Low	Low	No information for multiple domains and risk of selection bias due to inclusion of patients with previous treatment of lung cancer (surgery and SBRT).
Bongers, 2011[286] N/A Fair	NA	Medium	Low	Low	Low	Medium	Low	Risk of outcome measurement bias; a "high proportion" of patients returned to their pulmonology outpatient clinics (number not reported) for longer-term followup; unclear how many patients or how their referring institutions collected data about chest wall toxicity that could be used in this analysis.
Brooks, 2017[204] NA Fair	NA	Low	Low	NI	NI	Low	Low	Sparse information was reported for multiple domains; it is unclear what the data source was for survival outcomes.

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First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Brunelli, 2015[181] NA Good	NA	Low	Low	NI	Low	Low	Low	NA
Bryant, 2018[196] VINCI: 2006-2015 Fair	NA	Low	Medium	NI	Medium	Low	Low	Potential misclassification of surgical approach subtype or bias related to missing data.
Byrne, 2008[161] PLuSS Fair	NA	Medium	Low	Low	Medium	Medium	Low	Risk of selection bias, missing data, and outcome measurement
Chang, 2007[192] SEER: 1988-1997 Fair	NA	Low	Low	NI	NI	Low	Low	No information from multiple domains.
Chang, 2012[282] N/A Fair	NA	Low	Low	Medium	NI	Low	Low	Deviation from the SBRT protocol for patients with centrally located tumors close to critical structures; no information about whether any patients were excluded during sample selection.
Chung, 2017[132] NLST Good	Low	Medium	Low	Low	Low	Low	Low	NA
Cox, 2003[154] Mayo Lung Project Fair	NA	Medium	Low	Low	Low	Medium	Low	Risk of selection and outcome measurement bias
Cox, 2017[186] NCDB: 2003-2006 Fair	NA	Low	Low	NI	NI	NI	Low	No information reported for several ROB domains.
Crabtree/ Timmeran, 2013,[265] 2010[272] RTOG 0236 Good	NA	Low	Low	Low	NI	Low	Low	NA
Crucitti, 2015[111] “Un repiro per la vita” Good	NA	Low	Low	Low	NI	Low	Low	NA

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First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Cummings, 2018[233] N/A Fair	NA	Low	Low	NI	NI	Medium	Medium	Risk of outcome measurement bias due to ascertainment methods and a short followup period in the single-fraction SBRT arm; risk of selective outcome reporting bias in that Grade 1-2 toxicities were not recorded or reported.
Detillon, 2019[231] Netherlands Cancer Registry Fair	NA	Medium	Medium	NI	NI	Low	Low	Risk of selection bias in that nearly half of the sample (48%) lacked histological confirmation of NSCLC; no information reported about SBRT dosing used to treat the sample.
Dhanasopon, 2017[386] NCDB, 2004-2013 Poor	Medium	High	Low	Low	High	Low	Low	Risk of selection bias due to confounding by indication, and bias due to missing data, in that some patients were excluded from the analysis for missing data, but the authors did not report how many.
Dunn, 2017[163] UKLS Fair	Medium	Medium	Low	Low	Low	Low	Low	Risk of confounding and selection bias.
Dziedzic, 2017[217] Polish National Lung Cancer Registry Fair	NA	Medium	Low	NI	Medium	Low	Low	Risk of selection bias in that a "significant number of patients" did not receive PET staging of their tumors; ROB due to exclusion of patients with missing or "inconsistent" data without details about the criteria for that process.
Eba, 2016[201] NA Fair	NA	Low	Low	NI	Low	NI	Medium	Lack of information on multiple domains; risk of reporting bias due to the identification of 3-yr OS as the primary endpoint but the reporting of results for 5-yr OS.
Ezer, 2018[273] SEER: 2000-2009 Fair	NA	Low	Low	NI	NI	Low	Low	No information from multiple domains, including deviation from intended intervention and missing data.

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First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Fair	NA	Low	Low	NI	NI	Medium	Low	Risk of outcome measurement bias that may have led to an underestimation of toxicity events due to the study's short median followup time, reliance on retrospective review of hospital medical records for some ascertainment, and small sample (N=74 patients with 78 tumors).
Fernandez, 2012[188] SEER-Medicare: 1998-2005 Fair	NA	Low	Low	NI	NI	Low	Low	No information on multiple domains.
Ferrero, 2015[262] NA Fair	NA	NI	Low	Low	Medium	Low	Low	Medium ROB due to missing data over the course of followup and no information on potential sources of selection bias.
Fischer-Valuck, 2013[281] N/A Fair	NA	Low	Low	Low	NI	NI	Low	No or minimal information on multiple domains.
Gareen, 2014[156] NLST Fair	NA	Medium	Medium	Low	Low	Low	Medium	Risk of selection bias because selection was related to outcome, but with adjustment. Potential for selective reporting bias in that results are inconsistent with a priori plan.
Goya, 2005[195] Japanese Joint Committee of Lung Cancer Registry Fair	NA	Medium	Low	NI	Low	NI	Low	Potential selection bias as the type of hospital may be related to survival outcomes; little information reported about the source(s) of the data from individual hospitals.
Grills, 2012[256] NA Fair	NA	Medium	Medium	Low	NI	Low	Low	Risk of selection and intervention classification bias across multiple institutions; lack of information on missing data; unclear how harms were included or excluded in the reporting

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First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Guckenberger, 2013[280] N/A Fair	NA	Medium	Low	NI	Medium	Medium	Low	Risk of selection bias because the study may have included patients with secondary tumors; exclusion of one of 13 centers from the toxicity analysis may have introduced bias related to missing data; risk of measurement bias because not all participating centers had in-house databases for managing the data of SBRT patients; no information about adherence to SBRT protocols.
Guerrera, 2015[171] NA Fair	NA	Low	Low	Low	NI	NI	Low	Lack of information for several domains.
Haasbeek, 2010[291] N/A Fair	NA	Medium	Low	Low	NI	Medium	Low	Risk of selection bias in that majority of sample (61%) lacked histological confirmation of NSCLC; risk of outcome measurement bias due to a short median followup period and some reliance on referring lung physicians or GPs for the toxicity data of patients opting out of followup at the study center.
Haidar, 2014[257] NA Fair	NA	Low	Low	Low	Medium	Low	Low	Some missing data related to pathologic confirmation of disease.
Handa, 2018[218] N/A Fair	NA	Low	Low	NI	NI	Medium	Low	Risk of outcome measurement bias because of reliance on a single hospital's existing data; no information from multiple domains.
Henschke, 2006[128] I-ELCAP Fair	NA	Medium	Low	Low	Medium	Low	Low	Patient selection, decreased patients in annual screening
Henschke, 2006[129] I-ELCAP Fair	NA	Medium	Low	Low	Low	Low	Low	Risk of selection bias

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Henschke, 2006[131] I-ELCAP Fair	NA	Medium	Low	Low	Low	Low	Low	Risk of selection bias
Henschke, 2013[107] I-ELCAP Good	NA	Low	Low	Low	Low	Low	NI	NA
Heuvelmans, 2015[325] NELSON Fair	NA	Low	Low	Low	Low	Medium	Medium	Risk of outcome measurement bias; unclear if assessments were done with knowledge of patient's position in study; risk for selective reporting bias.
Husain, 2015[239] NCDB: 2003-2011 Fair	NA	Low	Low	Low	NI	Low	Medium	No information on missing data and potential for reporting bias with limited harms data reported.
Infante, 2011[140] DANTE Fair	NA	Medium	Low	Low	Low	Low	Medium	Risk of selection bias because enrollment was related to outcome; risk of outcome measurement bias because unclear if assessment done with knowledge of patient's position in study; risk of selective reporting bias in that outcomes were inconsistent with a priori plan.
Inoue, 2013[224] N/A Fair	NA	Low	Low	Low	NI	Medium	Low	Risk of outcome measurement bias with short followup period for survival outcomes; no information about missing data.
Jeon, 2018[268] NA Fair	NA	Low	Low	Low	NI	Low	Low	No information related to missing data. Authors retrospectively analyzed data that seemed to have been collected prospectively, but there is minimal description of the data ascertainment methods employed.

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Jeppesen, 2013[223] N/A Fair	NA	Medium	Low	NI	NI	Low	Low	Missing information about multiple domains. Risk for selection bias in that some patients may have had Stage II cancer, depending on which classification system the investigators applied to the sample.
Jeppesen, 2018[203] NA Fair	NA	Low	Low	Low	NI	Medium	Medium	No information on missing data and potential for information bias related to outcomes, which were ascertained from medical records and only selectively reported.
Kaerlev, 2012[157] DLCST Good	NA	Low	Low	Low	Low	Low	Low	NA
Karasawa, 2018[229] N/A Fair	NA	Low	Low	Low	Medium	Medium	Low	Risk of bias from exclusion of 33% of eligible SBRT patients because of a dose difference due to a difference in calculation method; risk of outcome measurement bias.
Katoh, 2017[255] NA Fair	NA	Low	Low	Low	NI	Low	Medium	No information on missing data and very little information was provided on harms, except radiation pneumonitis, other than reporting that 1 grade 2 dermatitis and 10 grade 2 thoracic wall pain cases, no other toxicities were reported; data were not presented for Stage 1 patients only.
Khullar, 2015[178] NCDB: 2003-2006 Fair	NA	Low	Low	NI	NI	Low	Low	Lack of information for multiple domains.
Khullar, 2015[189] NCDB: 2003-2011 Fair	NA	Low	Low	NI	Medium	NI	Low	No information for several ROB domains. Patient characteristics are presented for the entire cohort of patients but not the subcohort that contributed to the long-term survival analyses.

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Kinsinger, 2017[38] VA Population (LCSDP) Fair	NA	Medium	NI	NI	Low	NI	Low	Risk of selection bias because not all eligible patients (veterans) participated
Koshy, 2015[200] NCDB: 2003-2006 Fair	NA	Medium	Low	Low	NI	Low	Low	Risk of selection bias (only 64% of patients receiving SBRT were included) and lack of information related to missing data.
Lagerwaard, 2008[292] N/A Fair	NA	Medium	Low	Low	NI	Medium	Low	Risk of selection bias because most patients lacked histopathological confirmation of NSCLC; unclear how many of the 18% of patients with a prior lung cancer were actually experiencing a secondary tumor or recurrence (vs. a primary tumor); risk of outcome measurement bias due to short median followup period and at least some reliance on referring lung physicians or GPs for toxicity data of patients opting out of followup at the study center.
Lagerwaard, 2012[283] N/A Fair	NA	Low	Low	Low	Medium	Medium	Low	Risk of bias due to missing data that may have affected toxicity results; HRQOL data were missing for a large percentage of patients at 18- and 24-month time points; unclear how many patients were missing toxicity data, but the reasons for attrition, such as patients returning to their local hospitals, likely also reduced the availability of toxicity data.

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Lagerwaard, 2012[225] N/A Fair	NA	Medium	Low	Low	NI	Medium	Low	Risk of selection bias in that probable operability of patients for selection into study was determined post hoc; risk of outcome measurement bias because investigators relied on referring physicians for toxicity data for an unknown number of patients opting out of followup at the study center.
Lakha, 2014[175] SEER: 2004-2010 Fair	NA	Low	Low	NI	NI	Low	Low	No information on multiple domains.
Lam, 2018[202] NCDB: 2004-2014 Fair	NA	Low	Low	NI	NI	NI	Low	No information provided related to several domains.
Landreneau, 2014[176] NA Fair	NA	Low	Low	NI	NI	Low	Low	Lack of information related to intervention deviation and missing data. The analysis was among propensity-score matched groups defined by surgical approach; this isn't a selection bias but might impact generalizability (e.g., unmatched had surgery earlier than matched, were less likely to have COPD, and had larger tumors).
Lee, 2015[387] RegulomeDB Poor	NA (KQs 6 & 7)	NI	NI	NI	NI	NI	NI	Uncontrolled study with very little information reported that was relevant to ROB assessment.
Lee, 2018[234] N/A Fair	NA	Low	Low	NI	Medium	Medium	Low	ROB due to exclusion of patients not followed up at the study's hospital, and also potential outcome measurement bias due to the post hoc nature of the analysis.

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Licht, 2013[249] DLCR: 2007-2011 Fair	NA	Medium	Low	Low	Low	Low	Low	Risk of selection bias because authors only included standard lobectomies in the study in an "attempt to make VATS and thoracotomy groups more comparable." Authors did not provide their definition of a nonstandard lobectomy.
Lindberg, 2015[207] NA Fair	NA	Low	Low	Low	NI	Low	Low	Lack of information on missing data.
Liu, 2018[219] SEER: 2000-2013 Fair	NA	Low	Low	NI	Medium	Low	Low	ROB due to missing data because patients were excluded for missing examinable lymph node counts and clinical features.
Louie, 2016[238] STS-GTS: 2009-2013 Fair	NA	Medium	Low	Low	NI	NI	Low	No information for multiple domains and potential selection bias resulting from exclusion of cases from low-volume centers.
Lutz, 2019[220] N/A Fair	NA	Low	Low	NI	Low	Medium	Low	No information on intervention deviation; risk of outcome measurement bias because no statistical methods or adjustments were used to explore the impact of including 140 patients (22.5% of the 621 in the study sample) who were upstaged in the analysis.
Lv, 2018[221] SEER: 2004-2014 Fair	NA	Low	Low	NI	NI	Low	Medium	No information from multiple domains; risk of reporting bias because the study's only eligible survival data, 5-year OS, were reported for the total sample, not the lobectomy or SLR arms, for which overall survival curves were compared.
Ma, 2017[269] NA Fair	NA	Low	Low	NI	NI	Low	Medium	Medium risk of reporting bias due to certain data points not being collected and no information on multiple other domains.

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Maeda, 2010[191] NA Fair	NA	Low	Low	NI	NI	Low	Low	No information on multiple domains.
Maeda, 2012[184] NA Fair	NA	Low	Low	NI	NI	Low	Low	No information on multiple domains.
Manyam, 2019[230] N/A Fair	NA	Low	Low	Low	NI	Medium	Low	Risk of outcome measurement bias for 5-year OS due to a short followup period (median 23.8 months).
Mascalchi, 2006[136] ITALUNG Fair	NA	Medium	Low	Low	Low	Low	Low	Risk of selection bias
Mathieu, 2014[260] NA Fair	NA	Low	Low	Low	Medium	Low	Medium	ROB related to exclusion of patients with disease recurrence from analysis and reporting of only some toxicities.
Matsuo, 2012[285] N/A Fair	NA	Low	Low	Low	NI	Medium	Low	No information on missing data; risk of outcome measurement bias in that the analysis was based on post hoc ascertainment.
Matsuo, 2014[198] NA Fair	NA	Medium	Low	NI	NI	Low	Low	No information for multiple domains and some concern over selection of patients given that the original trial was stopped early due to slow patient enrollment.
Mediratta, 2014[177] NA Good	NA	Low	Low	NI	Low	Low	Low	NA
Melvan, 2015[243] NCDB: 2003-2011 Fair	NA	Low	Low	NI	Medium	Low	Low	Medium ROB related missing data and no information on intervention deviation.
Menezes, 2010[121] NA Fair	NA	Medium	Low	Low	Medium	Low	Low	Unclear selection, poor followup after 1st annual screening

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Miura, 2015[388] NA Poor	NA	High	Low	Low	NI	Low	Low	Restricting the study sample to patients with at least 12 months of followup CT scans after SBRT (i.e., a minimum of 4 followup scans) introduces a high risk of selection bias; unclear why this criterion was applied since all radiation-induced rib fractures after the first day of SBRT were included; unclear how many cases of rib fractures were missed as a result of the exclusion. Additionally, more than half of the patients had multiple cancers (some lung, some other sites).
Moon, 2018[214] SEER: 2000-2014 Fair	NA	Low	Medium	NI	NI	Low	Low	ROB due to intervention classification in that it was unclear how many segmentectomy patients received "intentional" vs. "compromised" procedures based on their comorbidities, and potential bias due to lack of information about missing data.
Morgan, 2017[167] NA Fair	NA	Medium	NI	Low	Low	Low	Low	Risk of selection bias.
Mutter, 2012[287] N/A Fair	NA	Low	Low	Low	NI	Medium	Low	Risk of outcome measurement bias in that median followup time (16 months) was shorter than the median time to rib fracture diagnosis (27 months).
Nagata, 2015[205] JCOG0403 Fair	NA	Low	Low	NI	NI	Medium	Medium	Long-term followup methods unclear, lack of information on missingness of data, and potential reporting bias related to grade 1-2 harms.
Nakamura, 2015[173] NA Fair	NA	Low	Low	NI	NI	NI	Medium	Post hoc analysis focused on intraoperative blood loss and lack of information on multiple domains.

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Nguyen, 2016[166] NLST Fair	NA	Low	Low	Low	Low	NI	Low	Medium risk of selection bias due to possible healthy-volunteer bias, and potential outcome measurement bias because definition of "potentially significant" extrapulmonary findings was left up to radiologists interpreting CT scans to decide.
Nyman, 2016[267] SPACE† Fair	NA	Low	Low	Medium	Medium	Low	Low	A small percentage of patients did not receive SBRT as intended, data sources are unclear, and there is some missing data, though it is not thoroughly described.
Okada, 2006[193] NA Fair	NA	Low	Low	Medium	NI	Low	Low	ROB related to deviations from intended surgical approach and unknown attrition/missing data.
Olsen, 2011[288] N/A Fair	NA	Low	Low	Low	NI	Medium	Low	Risk of outcome measurement bias in that median followup time (range of 11 to 16 months) was short and may not have been enough time for some toxicity events to occur.
Onishi, 2007[226] N/A Fair	NA	Low	Low	NI	NI	Medium	Low	Potential risk of outcome measurement bias due to post hoc use data from 14 different hospitals. Missing information on multiple domains.
Palma, 2010[289] Amsterdam Cancer Registry Fair	NA	Medium	Medium	NI	NI	Medium	Low	Risk of selection bias due to lack of histologic confirmation of NSCLC among 33% of RT patients (and unknown proportion of those receiving SBRT). At least some risk of intervention misclassification because no dosing information was available for RT treatments given. Post hoc analysis of data from population-based registry. No information for several domains.
Pegna, 2013[99] ITALUNG Good	NA	Low	Low	Low	Low	Low	Low	NA

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Pinsky, 2014[64] NLST Fair	NA	Low	Low	Low	Low	Low	Medium	Post hoc analysis
Pinsky, 2015[100] NLST Fair	NA	Medium	Low	NI	NI	Medium	Low	Medium risk of outcome measurement bias because of difference in how radiologists were instructed to assess nodule growth using Lung-RADS criteria vs. NLST criteria. They applied Lung-RADS criteria in a post-hoc fashion to patients previously screened using NLST criteria, which created the potential for discrepancy in terms of how nodes discovered at baseline were later classified as having growth during post-baseline scans. A sensitivity analysis was done assuming that all nodules reported with growth in NLST met Lung-RADS criteria for growth, but that assumption may have been incorrect in at least some cases.
Puri, 2014[242] NA Fair	NA	Low	Low	NI	NI	Low	Low	Lack of information for multiple domains. This is a post hoc analysis of two trial datasets that prospectively collected data.
Puri, 2015[252] NCDB: 1998-2010 Fair	NA	Medium	Low	Medium	NI	Low	Medium	Risk of selection bias in terms of the patients that completed followup; authors were unable to explain the large difference in median survival between the surgical and SBRT groups. No information provided on missingness of data. Author utilized propensity-score matching to compare surgery to SBRT, but results were only presented for surgery overall and SLR.
Pinsky, 2018[139] NLST Fair	Medium	Low	Low	Low	Low	Medium	Low	Post hoc analysis of NLST RCT, looking at intervention arm of study.

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Rampinelli, 2017[134] COSMOS Fair	Yes	Low	Low	Low	NI	NI	NI	Bias due to the source of harms data; data on the harm of radiation-induced cancer from LDCT program were estimated (not measured) based on an assumed relationship (which in turn is based on data from other studies of radiation therapy) that appears to be controversial.
Razi, 2016[180] SEER: 1998-2007 Fair	NA	Low	Low	NI	NI	Low	Low	Lack of information for multiple domains.
Robinson, 2013[266] NA Fair	NA	Low	Low	NI	NI	NI	Low	There was no information for several domains.
Rosen, 2014[244] NCDB: 2004-2009 Fair	NA	Low	Low	NI	Medium	Low	Low	Medium ROB related to missing data (both in terms of how missingness of some variables resulted in exclusion from study and in unknown stage data) and lack of information on intervention deviation.
Rosen, 2014[258] NA Fair	NA	Low	Low	Low	NI	Low	Medium	Risk of reporting bias and lack of information on missing data.
Rosen, 2016[185] NCDB: 2008-2012 Good	NA	Low	Low	Low	NI	Low	Low	NA
Samson, 2015[240] NCDB: 1998-2010; Washington SOM 2000-2012 Fair	NA	Low	Low	NI	NI	NI	Low	Lack of information for several domains.

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Samson, 2017[245] NCDB: 2004-2013 Fair	NA	Medium	Low	NI	NI	Low	Low	Medium risk of selection bias and lack of information on several additional domains.
Sawabata, 2011[190] Japanese Joint Committee of Lung Cancer Registry Fair	NA	Low	Low	NI	Low	NI	Low	No information for multiple domains and few details provided by the authors, except as they related to tumor characteristics.
Scheel, 2015[170] NA Fair	NA	Low	Low	Low	NI	Medium	Low	No information on extent of missing data and potential for outcome misclassification.
Schuchert, 2012[248] NA Fair	NA	Medium	Low	NI	NI	Low	Low	Patients were identified from multiple databases, including billing records. Authors report that patients who received incomplete resections were not included; if incomplete resection is associated with poorer outcomes, there could be selection bias present. Lack of information related to several other domains.
Sekihara, 2018[222] N/A Fair	NA	Low	Low	NI	NI	Medium	Low	Risk of outcome measurement bias in that the study relied on a post hoc analysis of a single hospital's data, and no information from multiple domains.
Shapiro, 2012[247] SEER: 1992-2002 Fair	NA	Low	Low	NI	Medium	Low	Low	Medium ROB related to missing data.
Shibamoto, 2012[236] N/A Good	NA	Low	Low	Low	Low	Low	Low	NA

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Shirvani, 2012[237] SEER: 2001-2007 Fair	NA	Low	Low	NI	NI	Low	Low	No information on multiple domains.
Shirvani, 2014[241] SEER: 2003-2009 Fair	NA	Medium	Low	Low	NI	Low	Low	Risk of selection bias resulting from exclusion of patients with incomplete Medicare records. Lack of information on missing outcomes data.
Speicher, 2016[187] NCDB: 2003-2006 Fair	NA	Low	Low	NI	Medium	NI	Low	No information for several ROB domains. Patient characteristics are presented for the entire cohort of patients but not the subcohort that contributed to the long-term survival analyses.
Stanic, 2014[279] RTOG 0236 Fair	NA	Medium	Low	NI	Medium	Medium	Low	Risk of self-selection bias indicated by fact that most of the sample was female when majority of NSCLC patients in the population are male. Potential bias from missing data for PFT outcomes due to test noncompliance at each timepoint of interest. Potential bias from outcome measurement for PFT outcomes in that large variation occurred in the timing of assessments.
Stephens, 2014[182] NA Fair	NA	Low	Low	Medium	NI	Low	Low	ROB related to patients who crossed over from one surgical approach to another and lack of information related to missing data.
Stokes, 2018[251] NCDB: 2004-2013 Fair	NA	Medium	NI	NI	Low	NI	Low	No information provided related to several domains. Missing data informed selection of patients into the analysis (i.e., complete case analysis).
Strand, 2006[194] Cancer Registry of Norway Good	NA	Low	Low	Low	Low	Low	Low	NA

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Styn, 2009[151] PLuSS Fair	NA	Medium	Low	Low	Low	Medium	Low	Potential bias from outcomes and patient selection.
Su, 2014[174] ACOSOG Z0030 (Alliance) Fair	NA	Low	Low	NI	NI	Low	Low	Lack of information on several domains.
Sun, 2017[197] NA Fair	NA	Medium	Low	Low	Low	NI	Low	Risk of selection bias with respect to inclusion of patients with a prior history of lung or other cancers. Additionally, 5% of the enrolled patients had no followup imaging or records and were not included in the analysis.
Swensen, 2002[168] NA Fair	NA	Medium	Low	Low	Low	Low	Low	Potential bias from patient selection.
Swensen, 2005[130] NA Fair	NA	Medium	Low	Low	Medium	Low	Low	Potential bias from patient selection and missing data.
Taremi, 2012[261] NA Fair	NA	Medium	Low	NI	NI	Low	Low	Medium risk of selection bias related to short followup periods and lack of information related to missing data.
Taremi, 2012[264] NA Fair	NA	Low	Low	NI	NI	Low	Low	Lack of information for multiple domains.
Thalanayar, 2015[143] PLuSS Fair	NA	Medium	Low	Low	Low	Medium	Low	Potential bias due to patient selection and outcome.
Townsend, 2005[152] Mayo Lung Project Fair	NA	Medium	Low	Low	Medium	Medium	Low	Possible selection, outcome and missing data bias as listed.

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Toyoda, 2008[126] NA Fair	NA	Medium	Low	Low	Low	Low	Low	Potential bias due to patient selection.
Tsushima, 2008[123] NA Fair	NA	Medium	Low	Low	Low	Low	Low	Potential bias due to patient selection.
Tsutani, 2014[179] NA Good	NA	Low	Low	NI	Low	Low	Low	NA
Ubels, 2015[206] NA Fair	NA	Medium	Low	NI	NI	Low	Low	Lack of information for multiple domains. The study included a small number of patients; almost 10% of them were excluded after enrollment for reasons that may be associated with poorer outcomes.
Ueda, 2018[274] N/A Fair	NA	Low	Low	NI	NI	Medium	Low	No information in multiple domains; risk of outcome measurement bias because ECG was inconsistently used to identify POAF, the study's primary outcome of interest, and more broadly, this was a small post hoc analysis of a single hospital's data.
Uhlig, 2018[228] NCDB: 2004-2013 Fair	NA	Low	Low	NI	Low	Medium	Low	Risk of outcome measurement bias due to the post hoc nature of the analysis and lack of detail about systems for outcome ascertainment.
Valle, 2016[246] NCCN: 2007-2011 Fair	NA	Medium	Low	NI	Medium	NI	Low	Risk of selection bias and bias due to missing data; no information provided for additional domains.
Veronesi, 2008[124] COSMOS Fair	NA	Medium	Low	Low	Low	Low	Low	Risk of patient selection bias.
Veronesi, 2008[127] COSMOS Fair	NA	Medium	Low	Low	Low	Low	Low	Risk of selection bias.

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Veronesi, 2012[135] COSMOS Fair	Medium	Low	Low	Low	Medium	Medium	Medium	ROB likely affects the size of effects this study demonstrates: namely, that (for scenario A) greater VDT is associated with lower LC mortality (and likely overdiagnosis), as well as for scenario B) that LDCT screening finds indolent lesions, i.e., those with long VDT. Sources of bias include confounding, missing data, outcomes measurement, and selective reporting.
Videtic, 2014[271] NA Fair	NA	Medium	Low	Low	NI	Low	Low	Risk of selection bias and lack of information on missingness of data.
Wagnetz, 2012[118] NA Fair	NA	Medium	Low	Low	NI	Low	Low	Risk of selection bias and no information on missing data.
Walker, 2015[133] NA Fair	NA	Medium	Low	Low	Low	Low	Low	ROB due to patient selection.
Walter, 2016[78] NELSON Good	NA	Low	Low	Low	Low	Low	Low	NA
Westover, 2012[284] N/A Fair	NA	Low	Low	Low	Low	Medium	Low	Medium risk of outcome measurement bias; study relied on a database and drew data from a very small sample of 15 patients.
Wilson, 2008[137] PLuSS Fair	NA	Medium	Low	Low	Low	Low	Low	ROB due to patient selection.

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Wink, 2019[235] N/A Fair	NA	Medium	Medium	NI	NI	Medium	Low	Missing information for multiple domains; post hoc analysis with short followup period for 5-year OS (median 48.1 months for surviving patients); risk of outcome measurement bias; OS data were retrieved from national databases, and unclear how comprehensively they captured mortality; risk of selection bias because majority (68%) of sample did not have histologic confirmation of NSCLC; variation in how SBRT was planned across the study's treating institutions.
Yang, 2016[250] NCDB: 2010-2012 Fair	NA	Low	Low	NI	NI	NI	Low	No information on multiple domains. Authors report that outcomes of surgical approach were evaluated with intent-to-treat analysis but provide no additional information.
Ye, 2018[294] N/A Fair	NA	Medium	Low	Low	NI	Low	Low	Risk of selection bias in that nearly a fifth (19%) of SBRT patients lacked pathologic confirmation of NSCLC.
Yousaf-Khan, 2017[389] NELSON Poor	Low	Medium	Low	Low	Medium	Low	Low	High risk of self-selection bias for the fourth round of screening, the focus of this substudy. Enrollment of 78% of eligible patients from 3rd round of screening (about 70% of initial sample) and confirmation in the article that the fourth round's patients differed significantly from the initial sample in several ways (e.g., more current smokers in the fourth round).
Zhai, 2014[172] NA Fair	NA	Low	Low	NI	NI	Low	Low	Lack of information for several domains.
Zhao, 2014[109] NELSON Fair	NA	Low	Low	Medium	Low	Low	NI	This longitudinal study did not apply the same imaging followup protocol to all patients in terms of the intervals between scans.

Appendix D Table 1. Risk of Bias and Overall Quality Assessment Ratings for Nonrandomized Studies

First Author, Year Study Name Quality Rating	Confounding*	Participant Selection	Intervention Classification	Intervention Deviation	Missing Data	Outcome Measurement	Reporting	Comments for Fair- or Poor-Quality Studies
Zhao, 2017[183] SEER: 2004-2012 Fair	NA	Low	Low	NI	NI	Low	Low	Lack of information related to several domains.
Zhou, 2015[390] Mass General Hospital Database Poor	NA	High	Low	NI	Medium	NI	Medium	High risk of selection bias, medium ROB related to missing data/patient attrition and reporting of harms (i.e., 'complications'), and lack of information on additional domains.
Zhou, 2018[215] SEER: 2004-2013 Fair	NA	Medium	Low	NI	Low	Low	Low	Risk of selection bias because no detail was given about how patients' cancers were staged, and no information about potential deviation from intended interventions.

* Bias due to confounding did not apply to KQ6/7 studies.

† Only the SBRT arm of the study was eligible for this review.

Abbreviations: ACOSOG=American College of Surgeons Oncology Group; CHISEL=A Randomised Phase III Trial of Highly Conformal Hypofractionated Image Guided ("Stereotactic") Radiotherapy (HypoRT) Versus Conventionally Fractionated Radiotherapy (ConRT) for Inoperable Early Stage I Non-small Cell Lung Cancer; COPD=chronic obstructive pulmonary disease; COSMOS=Continuous Observation of Smoking Subjects study; CT=computed tomography; DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology trial; DLCR=Danish Lung Cancer Registry; ECG=electrocardiogram; GP=general practitioner; HRQOL=health-related quality of life; I-ELCAP=International Early Lung Cancer Action Project; ITALUNG=The Italian Lung Study; JCOG=Japan Clinical Oncology Group; KQ=Key Question; LC=lung cancer; LDCT=low-dose computed tomography; LCSDP=Lung Cancer Screening Demonstration Project; Lung-RADS=ACR Lung Imaging Reporting and Data System; NA=not applicable; NCCN=National Comprehensive Cancer Network; NCDB=National Cancer Database; NELSON=Dutch-Belgian Randomized Lung Cancer Screening Trial; NI=no information; NLST=National Lung Screening Trial; OS=overall surgery; PFT=pulmonary function test; POAF=postoperative atrial fibrillation; RCT=randomized, controlled trial; ROB=risk of bias; RT=radiotherapy; RTOG=Radiation Therapy Oncology Group; SBRT=stereotactic body radiation therapy; SEER=Surveillance, Epidemiology, and End Results; SLR=sublobar resection; SOM=School of Medicine; SPACE=Stereotactic Precision And Conventional Radiotherapy Evaluation; STS-GTS=Society of Thoracic Surgeons General Thoracic Surgery Database; VATS=video-assisted thoracoscopic surgery; VDT=volume doubling time; VINCI=Veteran's Affairs Informatics and Computing Infrastructure; vs.=versus.

Appendix D Table 2. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 1

First Author, Year Study Name Quality Rating	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Eligibility criteria specified?	Were outcome measurements equal, reliable and valid?	Were outcome accessors masked?	Were care providers masked?	Were Patients masked?
Aberle, 2011[32] NLST Good	Yes	Yes	Yes	Yes	Yes	LC mortality: Yes LC incidence: unclear (but likely)	Unclear (but unlikely)	No
Aberle, 2013[58] NLST Good	Yes	Yes	Yes	Yes	Yes	LC mortality: Yes LC incidence: Unclear (but likely)	Unclear (but unlikely)	No
Aggestrup, 2012[160] DLCST Fair	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Ashraf, 2009[145] DLCST Fair	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Ashraf, 2014[147] DLCST Good	Yes	Unclear	Yes	Yes	Yes	Unclear (but unlikely to bias smoking cessation)	Unclear (but unlikely to bias smoking cessation)	No
Becker, 2012[60] LUSI Good	Yes	Unclear	Yes	Yes	Yes	NR	No (but unlikely to bias baseline screening results)	No
Becker, 2015[59], 2019[73] LUSI Fair	Yes	Unclear	Yes	Yes	Yes	NR	No	No
Brain, 2016[391] UKLS Poor	Yes	Yes	Yes	Yes	Yes	NR	No	No
Brain, 2017[392] UKLS Poor	Yes	Yes	Yes	Yes	Unclear	Not reported	No	No
Church, 2013[57] NLST Good	Yes	Yes	Yes	Yes	Yes	LC mortality: Yes LC incidence: Unclear (but likely)	Unclear (but unlikely)	No
Clark, 2016[149] NLST Fair	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear (but unlikely)	No

Appendix D Table 2. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 1

First Author, Year Study Name Quality Rating	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Eligibility criteria specified?	Were outcome measurements equal, reliable and valid?	Were outcome accessors masked?	Were care providers masked?	Were Patients masked?
Croswell, 2010[119] NA Fair	Yes	Yes	Yes	Yes	Yes	No	No	No
De Koning, 2020[76]	Yes*	Yes*	Yes	Yes	Unclear	Yes	Unclear	No
Field, 2016[97] UKLS Fair	Yes	Unclear	Yes	Yes	No	Unclear	Unclear	No
Field, 2016[117] UKLS Fair	Yes	Yes	Yes	Yes	Yes	NR	No	No
Gohagan, 2004[70] LSS Fair	Yes	Yes	Yes	Yes	Yes	No	No	No
Gohagan, 2005[69] LSS Fair	Yes	Yes	Yes	Yes	Yes	No	No	No
Heleno, 2018[141] DLCST Fair	Yes	NR	Mostly (slightly higher risk)	Yes	Yes	NR	No	No
Horeweg, 2013[98] NELSON Poor	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	No
Horeweg, 2014[33] NELSON Poor	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	No
Infante, 2008[72] DANTE Fair	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Infante, 2009[71] DANTE Fair	Yes	Yes	Yes	Yes	Yes	Unclear	No	No

Appendix D Table 2. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 1

First Author, Year Study Name Quality Rating	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Eligibility criteria specified?	Were outcome measurements equal, reliable and valid?	Were outcome accessors masked?	Were care providers masked?	Were Patients masked?
Infante, 2015[61] DANTE Fair	Yes	No	Yes	Yes	Yes	Unclear	Unclear	No
Lopes Penga, 2009[125] ITALUNG Fair	Yes	Yes	Yes	Yes	Yes	No	No	No
National Lung Screening Trial Research Team, 2019[74] NLST Fair	Yes	Yes	Yes	Yes	Unclear; ascertainment methods differed for trial years (when outcome verification committee was involved) and post-trial years	Unclear	Unclear (but unlikely)	No
O'Grady, 2014[169] PLCO, NLST Good	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Paci, 2017[62] ITALUNG Fair	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Pastorino, 2012[80] and 2019[75, 81] MILD Poor	No	Unclear	No	Yes	Unclear	Unclear	No	No
Patz, 2014[142] NLST Fair	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Pedersen, 2009[122] DLCST Good	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Pinsky, 2005[393], Doroudi, 2018[75] LSS Fair	Yes	Yes	Yes	Yes	Yes	No	No	No

Appendix D Table 2. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 1

First Author, Year Study Name Quality Rating	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Eligibility criteria specified?	Were outcome measurements equal, reliable and valid?	Were outcome accessors masked?	Were care providers masked?	Were Patients masked?
Pinsky, 2013[63] NLST Fair	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Rasmussen, 2014[158] DLCST Fair	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Saghir, 2012[65] DLCST Fair	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Sverzellati, 2016[82] MILD Fair	Yes (for annual vs. Biennial)	Unclear	Yes	Yes	Yes	Unclear	No	No
Tanner, 2015[66] NLST Fair	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Taylor, 2007[155] NLST/LSS Fair	Yes	Yes	Yes	Yes	Yes	No	No	No
van den Bergh, 2010[162] NELSON Fair	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
van den Bergh, 2011[159] NELSON Fair	Yes	Yes	Yes	Yes	Unclear	Yes	No	No
van der Aalst, 2010[148] NELSON Fair	Yes	Yes	Yes	Yes	Yes	No	No	No
van der Aalst, 2011[153] NELSON Fair	Yes	Yes	Yes	Yes	Yes	No	No	No
van Klaveren, 2009[120] NELSON Good	Yes	Yes	Yes	Yes	Yes	No	No	No

Appendix D Table 2. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 1

First Author, Year Study Name Quality Rating	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Eligibility criteria specified?	Were outcome measurements equal, reliable and valid?	Were outcome accessors masked?	Were care providers masked?	Were Patients masked?
van't Westeinde, 2012[138] NELSON Fair	Yes	Yes	Yes	Yes	Yes	No	No	No
Videtic, 2015[263] RTOG 0915 Fair	Unclear	Unclear	Unclear	Yes	Yes	Unclear	No	No
Wille, 2016[67] DLCST Good	Yes	Yes	Yes	Yes	Yes	Unclear	No	No
Young, 2015[144] NLST Fair	Yes	Yes	Yes	Yes	Yes	Yes	No	No

***** Details of randomization and allocation concealment were not published but were obtained by written personal communication from the first author. In short, all invited persons were given an 8-character random number by an external consultant. For persons responding with informed consent, these personal identification numbers were shifted by 1-8 positions (blindly, randomly computer generated), and then sorted again (ascending numbers) to be randomized. No investigator had control nor insight into this random process, and it also ensured that the consultant could not influence this process.

Abbreviations: CT=computed tomography; DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology trial; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=The Italian Lung Study; LC=lung cancer; LUSI=German Lung Cancer Screening Intervention Trial; MILD=Multicentric Italian Lung Detection trial; NELSON=Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST=National Lung Screening Trial; NR=Not reported; PLCO=Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RTOG=Radiation Therapy Oncology Group; UKLS=UK Lung Cancer Screening trial; vs.=versus

Appendix D Table 3. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 2

First Author, Year Study Name Quality Rating	What was the reported adherence to the intervention?	Did the study have crossovers or contamination?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition >10% or overall high attrition, raising concerns for bias?
Aberle, 2011[32] NLST Good	CT: 95% CXR: 93%	Minimal (average annual rate of CT in CXR group: 4.3%)	Average over three screening rounds: 6.1%	Average over three screening rounds: LDCT: 5% CXR: 7% T0: LDCT: 1.5% CXR: 2.6% T1: LDCT: 6.0% CXR: 8.8% T2: LDCT: 7.1% CXR: 10.6%	No
Aberle, 2013[58] NLST Good	T1: LDCT: 94% CXR: 91.2% T2: LDCT: 92.9% CXR: 89.4%	NR for T1 and T2 screens; over three rounds, 4.3% (per Aberle 75)	Overall: T1: 7.4% T2: 8.8%	T1: LDCT: 6.0% CXR: 8.8% T2: LDCT: 7.1% CXR: 10.6%	No
Aggestrup, 2012[160] DLCST Fair	94.3%	NR	5.6%	CT: 2.9% Control: 8.2%	No
Ashraf, 2009[145] DLCST Fair	NR	NR	8.3%	CT: 5.3% Control: 11.6%	11.6% of the control group had missing data
Ashraf, 2014[147] DLCST Good	Year 5: 89% CT: 90% Control: 89% (Higher for years 1-4)	Yes	Year 5: 14.6%	CT: 6% Control: 12%	No Sensitivity analysis complete case vs. imputation LOCF same results
Becker, 2012[60] LUSI Good	CT: 99.9% Control: 99.9%	No (baseline screen)	0% (baseline screen)	None	No

Appendix D Table 3. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 2

First Author, Year Study Name Quality Rating	What was the reported adherence to the intervention?	Did the study have crossovers or contamination?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition >10% or overall high attrition, raising concerns for bias?
Becker, 2015[59], 2019[73] LUSI Fair	Year 3: CT: 93.4% Control: 94.5% Year 2: CT: 94.6% Control: 91.5% Year 1: CT: 99.9% Control: 99.9%	NR	Over five years: 0.1% - 6.9%	Year 3: CT: 6.6% Control: 5.5% Year 2: CT: 5.4% Control: 8.5% Year 1: CT: 0.1% Control: 0.1%	No
Brain, 2016[391] UKLS Poor	For psychosocial outcomes, adherence to followup surveys: T0: 99.9% T1: CT: 84% Control: 78% T2: CT: 82% Control: 65%	NR	For psychosocial outcomes: T0: 0.01% T1: CT: 16% Control: 22% T2: CT: 18% Control: 35%	Psychosocial outcomes: T0: 0.01% T1: CT: 16% Control: 22% T2: CT: 18% Control: 35%	Yes
Brain, 2017[392] UKLS Poor	For smoking cessation outcomes, adherence to followup surveys: T1: 65% T2: 57%	NR	T1: 35% T2: 43%	T1: CT: 31% Control: 39% T2: CT: 35% Control: 51%	Yes
Church, 2013[57] NLST Good	98%	NR for baseline scree, over three rounds, 4.3% (per Aberle 75)	2%	LDCT: 1.5% CXR: 2.6%	No
Clark, 2016[149] NLST Fair	NR for this subset of ACRIN centers; likely >90% given overall study adherence	NR for ACRIN centers subset; but for overall study 4.3%	NR for ACRIN center subset; likely similar to overall study	NR	No
Croswell, 2010[119] NA Fair	84.2%	NR	15.8%	CT: 15.8%	Yes

Appendix D Table 3. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 2

First Author, Year Study Name Quality Rating	What was the reported adherence to the intervention?	Did the study have crossovers or contamination?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition >10% or overall high attrition, raising concerns for bias?
De Koning, 2020[76]	90% among men for all rounds (95.8% for round 1 of screening); NR for women	Unclear	Missing data <2% for the primary outcome from linkages with national registries	<2%	No
Field, 2016[97] UKLS Fair	98.30%	NR	1.70%	Unclear	Unclear
Field, 2016[117] UKLS Fair	98%	NR	For psychosocial outcomes: T0: 0.01% T1: CT: 16% Control: 22% T2: CT: 18% Control: 35%	For psychosocial outcomes: Baseline: 0% T1 (2 weeks after LDCT or control notification): 6% T2 (10–27 months): 17%	T1: No T2: Yes
Gohagan, 2004[70] LSS Fair	95.5%	0.90%	4.5%	CT: 4.5%	No
Gohagan, 2005[69] LSS Fair	85.8%	NR	14.2%	CT: 14.2%	Yes
Heleno, 2018[141] DLCST Fair	NR	Yes	NR	NR	No
Horeweg, 2013[98] NELSON Poor	For all three waves: ~90-95%	Unclear	3.80%	Unclear	Unclear
Horeweg, 2014[33] NELSON Poor	90%	NR	3.80%	Unclear	Unclear
Infante, 2008[72] DANTE Fair	Baseline only: 100%	No	0%	0%	No

Appendix D Table 3. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 2

First Author, Year Study Name Quality Rating	What was the reported adherence to the intervention?	Did the study have crossovers or contamination?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition >10% or overall high attrition, raising concerns for bias?
Infante, 2009[71] DANTE Fair	90.9%	<10% (presented as combined arms needing CT)	9.1%	CT: 9.1%	No
Infante, 2015[61] DANTE Fair	94%	Yes	6%	Unclear	NA
Lopes Penga, 2009[125] ITALUNG Fair	87.2%	NR	12.7%	CT: 12.7%	Yes
National Lung Screening Trial Research Team, 2019[74] NLST Fair	NR in this article, and post-trial screening was unclear, but original NLST reported CT: 95% CXR: 93%	Unclear; post-trial screening was not ascertained	11/33 centers (representing 12.4% of trial participants) did not have a home state cancer registry for linkage for lung cancer incidence; for mortality, linkage to national death index was available for all but 2.2%	NR	Unclear for lung cancer incidence; no for lung cancer mortality and all-cause mortality
O'Grady, 2014[169] PLCO, NLST Good	High	Some	Unclear	Unclear	Unclear
Paci, 2017[62] ITALUNG Fair	Across 4 rounds of LDCT screening: 81%	Yes (but minimal)	Low (conducted ITT analysis)	Low	No

Appendix D Table 3. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 2

First Author, Year Study Name Quality Rating	What was the reported adherence to the intervention?	Did the study have crossovers or contamination?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition >10% or overall high attrition, raising concerns for bias?
Pastorino, 2012[80] and 2019[81] MILD Poor	>95%	Unclear for 5-year followup; by 10-year followup, 1.2% of control group had LDCT	Low (conducted ITT analysis) for loss to followup, but many people in control group had shorter followup duration.	Unclear for loss to followup, but less followup among control group (e.g., 44.9 vs. 56 months in 5-year followup study); percentage of subjects with available data at 10 years: 46.2% (805/1723) controls vs. 81.4% (1934/2376) LDCT	Yes, when considering differential followup, 35.2% fewer people from the control group had 10-year followup than in the LDCT group
Patz, 2014[142] NLST Fair	NR in this paper	NR	Low	No	No
Pedersen, 2009[122] DLCST Good	Unclear but appears to be 100% for baseline CT	NR	Number of CTs obtained NR	NR	It was NR whether any of the 2,052 patients did not have a CT
Pinsky, 2005[393] Doroudi, 2018[75] LSS Fair	85.8%	NR	14.2%	CT: 14.2%	Yes
Pinsky, 2013[63] NLST Fair	NR in this paper	NR	Low	No	No
Rasmussen, 2014[158] DLCST Fair	Unclear	Not much	Moderate for COS-LC	None at baseline, somewhat lower for COS-LC survey completion in control arm in subsequent rounds	Depends on which round of screening you are referring to
Saghir, 2012[65] DLCST Fair	High, mean annual participation 95.5%	Minimal	Low	Low	No
Sverzellati, 2016[82] MILD Fair	High, until years T5 and T6	NR	Low in early years, then moderate	Unclear	In later years, yes

Appendix D Table 3. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 2

First Author, Year Study Name Quality Rating	What was the reported adherence to the intervention?	Did the study have crossovers or contamination?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition >10% or overall high attrition, raising concerns for bias?
Tanner, 2015[66] NLST Fair	High in NLST	NR	Low	Low	No
Taylor, 2007[155] NLST/LSS Fair	79.7%	NR	20.3%	For entire survey group: 20.3%	Yes
van den Bergh, 2010[162] NELSON Fair	For all, 86.7% CT at T0: 91.0% (630/692) T1: 93.6% (641/685) T2: 93.0% (620/667) T3: 87.7% (600/684)	NR	13.3%	13.3%	Yes, at third annual screen
van den Bergh, 2011[159] NELSON Fair	NR in this paper	No	T0, All: 87.9% LDCT: 89.8% Control: 85.9% T1 Screen: 87.7% T2, All: 78.9% LDCT: 89.3%, Control 64.7%	LDCT: 89% vs. Control: 65%	Yes
van der Aalst, 2010[148] NELSON Fair	92.1%	No	NA	NA	NA
van der Aalst, 2011[153] NELSON Fair	92.1%	No	NA	NA	NA
van Klaveren, 2009[120] NELSON Good	96.4%	NR	3.5%	CT: 3.5%	No
van't Westeinde, 2012[138] NELSON Fair	NR in this publication (but >90% in other NELSON publications)	NR	NR	NR	NR

Appendix D Table 3. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 2

First Author, Year Study Name Quality Rating	What was the reported adherence to the intervention?	Did the study have crossovers or contamination?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition >10% or overall high attrition, raising concerns for bias?
Videtic, 2015[263] RTOG 0915 Fair	100% of analyzable patients	No	10/94 (11%) patients were excluded post-randomization due to withdrawal of consent, protocol violations, or RT dosing not met	34Gy group: 8/47 (17%) 48Gy group: 2/47 (4%)	Yes
Wille, 2016[67] DLCST Good	NR in this paper	No	Low	Low (LDCT: 20; Control: 14)	No
Young, 2015[144] NLST Fair	High in NLST	NR	Low	Low	No

Abbreviations: ACRIN=American College of Radiology Imaging Network; COS-LC=consequences of screening-lung cancer; CT=computed tomography; CXR=chest X-ray; DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology trial; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=The Italian Lung Study; ITT=intention-to-treat; LDCT=low-dose computed tomography; LOCF: last observation carried forward; LUSI=German Lung Cancer Screening Intervention Trial; MILD=Multicentric Italian Lung Detection trial; NA=not applicable; NELSON=Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST=National Lung Screening Trial; NR=not reported; PLCO=Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RTOG=Radiation Therapy Oncology Group; T=timepoint; UKLS=UK Lung Cancer Screening trial; vs.=versus.

Appendix D Table 4. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 3

First Author, Year Study Name Quality Rating	What was the method used to handle missing data?	Did the study use intention to screen analysis or ITT (e.g., rather than per protocol)?	Were ascertainment techniques for outcomes adequately described?	Were ascertainment techniques equal, valid, and reliable?	Overall Rating	Comments for Poor-Quality Studies
Aberle, 2011[32] NLST Good	NR, (small amount of missing data from baseline questionnaires) Missing data from Aberle 2010: 0.4%, similar each arm	Yes	Yes	Yes	Good	NA
Aberle, 2013[58] NLST Good	Missing data excluded from screening accuracy calculations	Yes	Yes	Yes	Good	NA
Aggestrup, 2012[160] DLCST Fair	NR	ITT	NR	NA	Fair	NA
Ashraf, 2009[145] DLCST Fair	Functioned under the assumption that they were still smokers	ITT	No	NA	Fair	NA
Ashraf, 2014[147] DLCST Good	Complete case and LOCF imputation	Yes	Yes	Yes	Good	NA
Becker, 2012[60] LUSI Good	Missing data NR, but baseline data appears complete	Yes	Yes	Yes	Good	NA
Becker, 2015[59], 2019[73] LUSI Fair	NR, but less than 10 participants each round were lost to followup, so complete case analysis would likely not bias results	Yes	Yes	Yes	Fair	NA

Appendix D Table 4. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 3

First Author, Year Study Name Quality Rating	What was the method used to handle missing data?	Did the study use intention to screen analysis or ITT (e.g., rather than per protocol)?	Were ascertainment techniques for outcomes adequately described?	Were ascertainment techniques equal, valid, and reliable?	Overall Rating	Comments for Poor-Quality Studies
Brain, 2016[391] UKLS Poor	For individual instruments: mean replacement imputation within domain if <35% missing data If > 35% missing data within domain, dropped from analysis. For participants lost to followup - complete case analysis. Sensitivity analysis performed where inverse probability weighting used to adjust for missing data	Yes	Yes	Yes	Poor	Poor quality rating is due to high attrition for psychosocial outcomes and greater loss to followup, as well as lack of reporting contamination and cross-overs in the control group.
Brain, 2017[392] UKLS Poor	Imputed all missing followup as smokers; sensitivity analysis of complete case with unclear use of inverse probability weighting to account for nonresponse	Yes	Yes	Yes	Poor	Poor quality rating due to high attrition for smoking cessation outcomes, single imputation conducted under the assumption that smoking status was positive, and unclear use of IPW
Church, 2013[57] NLST Good	Missing data excluded from screening accuracy calculations	Yes	Yes	Yes	Good	NA
Clark, 2016[149] NLST Fair	Complete case for smoking status data (5.8% missing followup forms)	Yes	Yes	Unclear	Fair	NA
Croswell, 2010[119] NA Fair	NR	No	NR	NA	Fair	NA
De Koning, 2020[76]	None (but missing data very low)	Yes	Mostly, but some details NR	Unclear	Fair	NA

Appendix D Table 4. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 3

First Author, Year Study Name Quality Rating	What was the method used to handle missing data?	Did the study use intention to screen analysis or ITT (e.g., rather than per protocol)?	Were ascertainment techniques for outcomes adequately described?	Were ascertainment techniques equal, valid, and reliable?	Overall Rating	Comments for Poor-Quality Studies
Field, 2016[97] UKLS Poor	Unclear	No	No	NA	Poor	Poor quality rating due to numerous unclear domains, including allocation concealment and accessor and provider masking, differential attrition, and methods used to handle missing data. No reporting on crossovers or contamination. This study did not report on the control arm
Field, 2016[117] UKLS Fair	Mean replacement strategy was used when participants were missing data for psychosocial variables	Yes	Yes	Yes	Fair	NA
Gohagan, 2004[70] LSS Fair	NR	No	NR	NA	Fair	NA
Gohagan, 2005[69] LSS Fair	NR	No	NR	NA	Fair	NA
Heleno, 2018[141] DLCST Fair	NR	Yes	Elsewhere	Presumably	Fair	NA
Horeweg, 2013[98] NELSON Poor	Did not include patients without a CT	No	No	NA	Poor	Poor quality rating due to numerous unclear domains, including allocation concealment, masking, crossover and contamination. No data from the control arm is reported in this study.
Horeweg, 2014[33] NELSON Poor	Excluded from analysis	No	No	NA	Poor	Poor quality rating due to lack of control arm inclusion, and because several groups were not reported due to unavailable data.
Infante, 2008[72] DANTE Fair	NR	Yes	NR	NA	Fair	NA

Appendix D Table 4. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 3

First Author, Year Study Name Quality Rating	What was the method used to handle missing data?	Did the study use intention to screen analysis or ITT (e.g., rather than per protocol)?	Were ascertainment techniques for outcomes adequately described?	Were ascertainment techniques equal, valid, and reliable?	Overall Rating	Comments for Poor-Quality Studies
Infante, 2009[71] DANTE Fair	NI	No	NR	NA	Fair	NA
Infante, 2015[61] DANTE Fair	Unclear	Yes	No	NA	Fair	NA
Lopes Penga, 2009[125] ITALUNG Fair	NR	No	NR	NA	Fair	NA
National Lung Screening Trial Research Team, 2019[74] NLST Fair	NR	Yes	Yes	Unclear for lung cancer incidence; yes for lung cancer mortality and all-cause mortality	Fair	NA
O'Grady, 2014[169] PLCO, NLST Good	Use of missing indicator variable	Yes	Yes	Yes	Good	NA
Paci, 2017[62] ITALUNG Fair	NA	Yes	Yes	Unclear (31 deaths of 335 in the trial underwent cause-of-death review; the other deaths did not undergo the same rigorous evaluation based on an algorithm with uncertain validity)	Fair	NA

Appendix D Table 4. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 3

First Author, Year Study Name Quality Rating	What was the method used to handle missing data?	Did the study use intention to screen analysis or ITT (e.g., rather than per protocol)?	Were ascertainment techniques for outcomes adequately described?	Were ascertainment techniques equal, valid, and reliable?	Overall Rating	Comments for Poor-Quality Studies
Pastorino, 2012[80] and 2019[81] MILD Poor	Unclear	Yes	No	Unclear	Poor	Poor-quality rating due to high risk of selection bias, unclear methods of randomization and allocation concealment, changing protocol and addition of a control arm later in the trial, lack of similar groups at baseline for important variables (e.g., proportion of current smokers), differential followup between groups, and high risk of measurement bias.
Patz, 2014[142] NLST Fair	NR in this paper	Yes	Yes	Yes	Fair	NA
Pedersen, 2009[122] DLCST Good	NR	Appears all had a CT in intervention arm	NR	NA	Good	NA
Pinsky, 2005[393] Doroudi, 2018[75] LSS Fair	NR	NR	NR	Unclear	Fair	NA
Pinsky, 2013[63] NLST Fair	NR in this paper	Yes	Yes	Yes	Fair	NA
Rasmussen, 2014[158] DLCST Fair	Imputation	Yes	Yes	Yes	Fair	NA
Saghir, 2012[65] DLCST Fair	NR	Yes	Yes	Yes	Fair	NA
Sverzellati, 2016[82] MILD Fair	NR in this paper	Unclear	Yes	Unclear	Fair	NA
Tanner, 2015[66] NLST Fair	NR	Yes	Yes (in other publications)	Yes	Fair	NA

Appendix D Table 4. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 3

First Author, Year Study Name Quality Rating	What was the method used to handle missing data?	Did the study use intention to screen analysis or ITT (e.g., rather than per protocol)?	Were ascertainment techniques for outcomes adequately described?	Were ascertainment techniques equal, valid, and reliable?	Overall Rating	Comments for Poor-Quality Studies
Taylor, 2007[155] NLST/LSS Fair	NR	No	NR	NA	Fair	NA
van den Bergh, 2010[162] NELSON Fair	Not used for each round	No	NR	NA	Fair	NA
van den Bergh, 2011[159] NELSON Fair	NR	Yes	Yes (in other publications)	Yes	Fair	NA
van der Aalst, 2010[148] NELSON Fair	NI	No	NR	NA	Fair	NA
van der Aalst, 2011[153] NELSON Fair	NI	No	NR	NA	Fair	NA
van Klaveren, 2009[120] NELSON Good	NI	No	NR	NA	Good	NA
van't Westeinde, 2012[138] NELSON Fair	Took only positive results from NELSON, thus missing data NR	No	NR	NA	Fair	NA
Videtic, 2015[263] RTOG 0915 Fair	Unclear	Yes	Yes	Yes	Fair	NA
Wille, 2016[67] DLCST Good	NA	Yes	Yes	Yes	Good	NA
Young, 2015[144] NLST Fair	NR in this paper	Yes	Yes (in other publications)	Yes	Fair	NA

Appendix D Table 4. Risk of Bias and Overall Quality Assessment Ratings for Randomized Studies: Part 3

Abbreviations: ACRIN=American College of Radiology Imaging Network; COPD=chronic obstructive pulmonary disease; CT=computed tomography; DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology trial; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=The Italian Lung Study; IPW=inverse probability weighting; ITT=Intention-to-treat; KQ=Key Question; LDCT=low-dose computed tomography; LOCF: Last observation carried forward; LUSI=German Lung Cancer Screening Intervention Trial; MILD=Multicentric Italian Lung Detection trial; NA=Not applicable; NELSON=Dutch-Belgian Randomized Lung Cancer Screening Trial; NI=Not included; NLST=National Lung Screening Trial; NR=Not reported; PLCO=Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RTOG=Radiation Therapy Oncology Group; UKLS=UK Lung Cancer Screening trial.

Appendix D Table 5. Risk of Bias and Overall Quality Assessment Ratings for Risk Prediction Model (KQ 2) Studies: Part 1

First Author, Year Model Name Quality Rating	Does study sample adequately capture the population of interest?	Was there selective inclusion of participants in the model based on data availability?	Enrolled consecutive patients or a random sample?	Selection criteria clearly described?	Was followup duration for the cohort the same as the time horizon of the prediction reported?	Is a valid and reliable definition and method for measurement of the outcomes reported?	Was the same outcome definition (and method for measurement) used in all patients?
De-Torres, 2015[88] COPD-LUCSS Fair	Maybe	Some	Yes	Yes	Yes	Yes	Somewhat
Katki, 2016[84] PLCO, NLST, NHIS Good	Yes	Some	Yes	Yes	Somewhat	Yes	Yes
Kovalckik, 2013[56] NLST Good	Yes	No	Yes	Yes	Yes	Yes	Yes
Landy, 2019[89] NHIS Fair	Yes (NHIS)	NR	No, complex sampling survey design	Yes, based on model development papers[84, 85]	NA – modeling study	NR/NA - modeling study	NA – modeling study
Li, 2015[394] EPIC Cohort Poor	No	Yes	No	Yes	No (only for 1 of the models)	Yes	Yes
Markaki, 2018[95] HUNT2 Cohort Fair	Yes	No	No. Entire county was sampled. 70% response rate	Yes	Yes, max followup 16 yrs. Two models estimated – 6 year and 16 year.	Yes, probably (although some uncertainty about validity and reliability of registry and ICD codes)	Yes
Tammemagi, 2013[85] PLCOm2012 Good	Yes	No	Yes	Yes	Yes	Yes	Yes
Tammemagi, 2014[87] NLST, PLCO Good	Yes	No	Yes	Yes	Yes	Yes	Yes
ten Haaf, 2017[83] NA Good	Yes	No	Yes	Yes	Yes	Yes	Yes

Appendix D Table 5. Risk of Bias and Overall Quality Assessment Ratings for Risk Prediction Model (KQ 2) Studies: Part 1

First Author, Year Model Name Quality Rating	Does study sample adequately capture the population of interest?	Was there selective inclusion of participants in the model based on data availability?	Enrolled consecutive patients or a random sample?	Selection criteria clearly described?	Was followup duration for the cohort the same as the time horizon of the prediction reported?	Is a valid and reliable definition and method for measurement of the outcomes reported?	Was the same outcome definition (and method for measurement) used in all patients?
Weber, 2017[86] PLCOm2012 Good	Yes	Some	Yes	Yes	Yes	Yes	Yes

Abbreviations: COPD=Chronic Obstructive Pulmonary Disease; COPD-LUCSS=COPD-Lung Cancer Screening Score; EPIC=European Prospective Investigation of Cancer and Nutrition; KQ=key question; NA=not applicable; NHIS=National Health Interview Survey; NLST=National Lung Screening Trial; PLCO=Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Appendix D Table 6. Risk of Bias and Overall Quality Assessment Ratings for Risk Prediction Model (KQ 2) Studies: Part 2

First Author, Year Model Name Quality Rating	Were the outcomes assessed without knowledge of the candidate predictors?	Are valid and reliable definitions and methods for measurement and classification of candidate predictor(s) reported?	Was the same predictor definition and method of measurement used in all patients?	Were all relevant predictors included?	Were predictors assessed blinded for the outcome, and for each other (if relevant)?	How were the predictors handled in the modelling?
De-Torres, 2015[88] COPD-LUCSS Fair	Yes	Yes	Yes	Yes	Yes	Categorized/dichotomized
Katki, 2016[84] PLCO, NLST, NHIS Good	Yes	Yes	Yes	Yes	Yes	Depends on predictor
Kovalckik, 2013[56] NLST Good	Yes	Yes for most (all historical/questionnaire) Unclear how NLST defined COPD/emphysema	Yes	Yes	Yes	Continuous for age, categorical for race/ethnicity, count for years since smoking cessation, first degree relatives with lung cancer, binary for sex, emphysema, and nonlinear for BMI
Landy, 2019[89] NHIS Fair	NA – modeling study	NR	NR	Yes, based on development papers[84, 85]	NA – modeling study	Refer to development papers[84, 85]
Li, 2015[394] EPIC Cohort Poor	NR	Yes	Yes	No (in this external validation, only for the Bach model were all predictors included)	Yes	Varies by model and predictor
Markaki, 2018[95] HUNT2 Cohort Fair	Probably yes (linkage to registry data on outcomes)	Probably yes (survey questions, although uncertain validity of that approach for hours of daily indoor exposure to smoke, which was in their final model)	Yes	Yes	Yes – prospective	Multiple ways (continuous cigarettes/day; log transformation – pack-years, years since quit, BMI, smoke exposure; p-spline transformation – age)

Appendix D Table 6. Risk of Bias and Overall Quality Assessment Ratings for Risk Prediction Model (KQ 2) Studies: Part 2

First Author, Year Model Name Quality Rating	Were the outcomes assessed without knowledge of the candidate predictors?	Are valid and reliable definitions and methods for measurement and classification of candidate predictor(s) reported?	Was the same predictor definition and method of measurement used in all patients?	Were all relevant predictors included?	Were predictors assessed blinded for the outcome, and for each other (if relevant)?	How were the predictors handled in the modelling?
Tammemagi, 2013[85] PLCOm2012 Good	Yes	Yes/No Self-reported demo, smoking	Yes/Unclear - most predictors are self-reported. - Unclear how COPD defined for NLST and PLCO (primary papers reviewed and no information - Oken and Aberle)	Yes	Yes	Continuous for age, BMI, education, duration smoking, smoking quit time, categorized for race/ethnicity, COPD, cancer history, family history cancer, smoking status, nonlinear transformation for smoking intensity
Tammemagi, 2014[87] NLST, PLCO Good	Yes	Yes	Yes	Yes	Yes	Continuous for age, BMI, education, duration smoking, smoking quit time, categorized for race/ethnicity, COPD, cancer history, family history cancer, smoking status, nonlinear transformation for smoking intensity
ten Haaf, 2017[83] NA Good	Yes	Yes	Probably- "data on predictor variables in each trial were collected through epidemiologic questionnaires administered at study entry and harmonized across both trials"	Yes	Yes	Nine models were considered. Refer to primary papers. (pull refs)
Weber, 2017[86] PLCOm2012 Good	Yes	Yes	Yes	Yes	Yes	Varies

Abbreviations: BMI=Body Mass Index; COPD=chronic obstructive pulmonary disease; COPD-LUCSS=COPD-Lung Cancer Screening Score; EPIC=European Prospective Investigation of Cancer and Nutrition; KQ=key question; NA=not applicable; NHIS=National Health Interview Survey; NLST=National Lung Screening Trial; NR=Not reported; PLCO=Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Appendix D Table 7. Risk of Bias and Overall Quality Assessment Ratings for Risk Prediction Model (KQ 2) Studies: Part 3

First Author, Year Model Name Quality Rating	Number (%) participants with missing data	Did the study have high attrition (>10%), raising concerns for bias?	How was missing data handled?	Modeling assumptions satisfied?	Describe the method for selection of predictors for inclusion in multivariable modelling	Describe the method for selection of predictors during multivariable modelling and criteria used
De-Torres, 2015[88] COPD-LUCSS Fair	Low	No	Imputation or assumption	NR	All	Significance in multivariable model, backwards selection
Katki, 2016[84] PLCO, NLST, NHIS Good	Less than 2%	No	Imputation or assumption	Yes	Previous models	Akaike and other
Kovalckik, 2013[56] NLST Good	From NLST parent paper < 1%	No	NR	Not reported	Based on prior studies	Lasso regression
Landy, 2019[89] NHIS Fair	1.8% for race/ethnicity, 0.4% for education, 2.9% for body mass index, 0.4% for number of years since quitting, 7.3% for number of cigarettes smoked per day, 0.3% for number of years of smoking, 0.2% for presence of emphysema, and 12.1% for family history of lung cancer	NA – modeling study	Multiple imputation	NR	Refer to development papers[84, 85]	Refer to development papers[84, 85]

Appendix D Table 7. Risk of Bias and Overall Quality Assessment Ratings for Risk Prediction Model (KQ 2) Studies: Part 3

First Author, Year Model Name Quality Rating	Number (%) participants with missing data	Did the study have high attrition (>10%), raising concerns for bias?	How was missing data handled?	Modeling assumptions satisfied?	Describe the method for selection of predictors for inclusion in multivariable modelling	Describe the method for selection of predictors during multivariable modelling and criteria used
Li, 2015[394] EPIC Cohort Poor	NR, although less than half of the EPIC cohort were included (20,700/53,088)	NR	Not reported for the outcomes; for predictors, they only included people with data for predictors and for the predictors that they had no data for in their cohort (e.g., COPD, pneumonia, emphysema, dust exposure, family history of lung cancer) they assumed that risk factors were absent	Not applicable - external validation only	Not applicable - external validation only (although see entry for missing data regarding how they didn't include all predictors from the original models)	Not applicable - external validation only
Markaki, 2018[95] HUNT2 Cohort Fair	9.35% total for all predictors	NR	Multiple imputation	NR	Authors selected risk factors for lung cancer and other smoking-related behaviors	Backwards selection; criteria not reported
Tammemagi, 2013[85] PLCOm2012 Good	PLCO < 5% for all predictors NLST < 1% for all predictors	No	NR; presumably complete case	Yes	Predictor selection guided by predictive performance, not based on univariate association p value	Predictor selection guided by predictive performance, not based on univariate association p value
Tammemagi, 2014[87] NLST, PLCO Good	< 5% missing per Oken 2011 and Kovalchik supplement (32)	Not reported, but per Oken 2011, overall adherence was high 91.2% of participants had undergone at least 1 CXR screen,	NR	Yes	Predictor selection guided by predictive performance, not based on univariate association p value	Predictor selection guided by predictive performance, not based on univariate association p value

Appendix D Table 7. Risk of Bias and Overall Quality Assessment Ratings for Risk Prediction Model (KQ 2) Studies: Part 3

First Author, Year Model Name Quality Rating	Number (%) participants with missing data	Did the study have high attrition (>10%), raising concerns for bias?	How was missing data handled?	Modeling assumptions satisfied?	Describe the method for selection of predictors for inclusion in multivariable modelling	Describe the method for selection of predictors during multivariable modelling and criteria used
ten Haaf, 2017[83] NA Good	<7% across all predictors	Probably No Reviewing primary studies: Aberle and Oken NLST <10% both arm PLCO intervention arm 16.5% PLCO control arm 8.8%	Multiple imputation	NR	NA - Model validation only	NA - Model validation only
Weber, 2017[86] PLCOm2012 Good	Low	No	Imputation or assumption	Yes	NA – Model validation only	NA – Model validation only

Abbreviations: COPD=chronic obstructive pulmonary disease; COPD-LUCSS=COPD-Lung Cancer Screening Score; CXR=chest X-ray; EPIC=European Prospective Investigation of Cancer and Nutrition; KQ=key question; NA=not applicable; NHIS=National Health Interview Survey; NLST=National Lung Screening Trial; NR=not reported; PLCO=Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

Appendix D Table 8. Risk of Bias and Overall Quality Assessment Ratings for Risk Prediction Model (KQ 2) Studies: Part 4

First Author, Year Study Name Quality Rating	Were a priori cut points used for classification measures?	Method used for testing model performance: development dataset only or separate external validation?	Were coefficients of final model published?	In case of poor validation, was the model adjusted or updated?	Was there comparison of the distribution of predictors for development and validation datasets?	Overall Rating	Comments for Poor Quality Studies
De-Torres, 2015[88] NLST Fair	Some	Separate, external	Yes	NA	Unclear	Fair	NA
Katki, 2016[84] PLCO, NLST, NHIS Good	Yes	Separate, external	Yes	NA	Yes	Good	NA
Kovalckik, 2013[56] NLST Good	NA	Development cohort: NLST CXR arm Validation cohort: PLCO CXR arm	No	NA	No	Good	NA
Landy, 2019[89] NHIS Fair	Yes	NA	Refer to development papers[84, 85]	NA	NA	Fair	NA
Li, 2015[394] EPIC Cohort Poor	No	Separate external validation	No	NA	NA	Poor	Concerns with missing data, missing predictor variables, selection of the sample, and changing the original models for analyses. Limited to ever smokers from among the larger cohort, introducing risk for bias.
Markaki, 2018[95] HUNT2 Cohort Fair	Yes	External validation	Yes	NA	NR	Fair	NA
Tammemagi, 2013[85] PLCOm2012 Good	No	External Validation	Yes	NA	Yes	Good	NA
Tammemagi, 2014[87] NLST, PLCO Good	No	External Validation	Yes	NA	Yes	Good	NA

Appendix D Table 8. Risk of Bias and Overall Quality Assessment Ratings for Risk Prediction Model (KQ 2) Studies: Part 4

First Author, Year Study Name Quality Rating	Were a priori cut points used for classification measures?	Method used for testing model performance: development dataset only or separate external validation?	Were coefficients of final model published?	In case of poor validation, was the model adjusted or updated?	Was there comparison of the distribution of predictors for development and validation datasets?	Overall Rating	Comments for Poor Quality Studies
ten Haaf, 2017[83] NA Good	No	External Validation	Review primary studies. PLCOm2012 has published coefficients	NA	Yes	Good	NA
Weber, 2017[86] PLCO, 2012 Good	Yes	Separate, external	Yes	NA	Unclear	Good	NA

Abbreviations: COPD=chronic obstructive pulmonary disease; COPD-LUCSS=COPD-Lung Cancer Screening Score; CXR=chest X-ray; EPIC=European Prospective Investigation of Cancer and Nutrition; KQ=key question; NA=not applicable; LC=lung cancer; LLP=Liverpool Lung Project; NHIS=National Health Interview Survey; NLST=National Lung Screening Trial; PLCO=Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; USPSTF=United States Preventive Services Task Force.

Appendix D Table 9. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 1

First Author, Year Study Name Quality Rating	Was a consecutive or random sample of patients used?	Was a case control design avoided?	Did the study avoid inappropriate exclusions?	Bias due to patient selection?	Were the test and reference standard results interpreted independently (blinded)?	If a threshold was used, was it pre-specified?	Were the tests adequately described (or referenced)?	Were methods for calculating accuracy clearly reported and valid?	Bias due to index test (LDCT)?
Aberle, 2011[32] NLST Good	Yes	Yes	Yes	Low	Yes	Yes	Yes	NA	Low
Aberle, 2011[58] NLST Good	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Becker, 2012[60] LUSI Good	Yes	Yes	Yes	Low	Yes	Yes	Yes	NA	Low
Becker, 2015[59] LUSI Good	Yes	Yes	Yes	Low	Yes	Yes	Yes	NA	Low
Chung, 2017[132] NLST Good	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Church, 2013[57] NLST Good	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Croswell, 2010[119] NA Fair	Yes	Yes	Yes	Low	Unclear	Yes	Yes	Yes	Low
Crucitti, 2015[111] “Un repiro per la vita” Fair/Poor	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes for false-positive screens	Low
De Koning, 2020[76]	Yes	Yes	Yes	Low	Yes	Yes	Yes	No	High
Field, 2016[97] UKLS Fair	Random	Yes	Yes	High	Unclear	Yes	Yes	Yes	Low
Field, 2016[117] UKLS Fair	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Gierada, 2017[110] NLST Fair	Yes (in parent trial)	No	Yes	Low	Not completely	Yes	Yes	Yes	Low

Appendix D Table 9. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 1

First Author, Year Study Name Quality Rating	Was a consecutive or random sample of patients used?	Was a case control design avoided?	Did the study avoid inappropriate exclusions?	Bias due to patient selection?	Were the test and reference standard results interpreted independently (blinded)?	If a threshold was used, was it pre-specified?	Were the tests adequately described (or referenced)?	Were methods for calculating accuracy clearly reported and valid?	Bias due to index test (LDCT)?
Gohagan, 2004[70] LSS Fair	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Low
Henschke, 2004[131] I-ELCAP Fair	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Low
Henschke, 2006[128] I-ELCAP Fair	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Low
Henschke, 2006[129] I-ELCAP Fair	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Low
Henschke, 2013[107] I-ELCAP Fair	Yes	Yes	Unclear	Low	Unclear	Multiple thresholds used	Yes	Yes	Low
Henschke, 2016[106] I-ELCAP Fair	Probably	Yes	Yes	Low	Yes	Yes	Yes	NA	Low
Heuvelmans, 2015[325] NELSON Poor	Random	Yes	Yes	Low	Unclear	Yes	Yes	Yes	Unclear
Heuvelmans, 2013[114] NELSON Fair	Yes	Yes	Yes	Low	Yes	No	Yes	Yes	Low
Horeweg, 2013[98] NELSON Fair	Random	Yes	Yes	Low	Unclear	Yes	Yes	Yes	Low

Appendix D Table 9. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 1

First Author, Year Study Name Quality Rating	Was a consecutive or random sample of patients used?	Was a case control design avoided?	Did the study avoid inappropriate exclusions?	Bias due to patient selection?	Were the test and reference standard results interpreted independently (blinded)?	If a threshold was used, was it pre-specified?	Were the tests adequately described (or referenced)?	Were methods for calculating accuracy clearly reported and valid?	Bias due to index test (LDCT)?
Horeweg, 2014[33] NELSON Fair	Random	Yes	No	Low	Unclear	Yes	No	Yes	High
Infante, 2009[71] DANTE Fair	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Low
Infante, 2015[61] DANTE Fair	Random	Yes	Yes	Low	Unclear	Yes	Yes	Yes	Low
Kinsinger, 2017[38] LCSDP Fair	No	Yes	NA	Unclear	NR	NR	Yes	Yes	Low
Lopes Penga, 2009[125] ITALUNG Fair	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Low
McKee, 2015[395] NA Poor	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
McWilliams, 2013[116] PanCan, BCCA Fair	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Menezes, 2010[121] NA Fair	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Low
Paci, 2017[62] ITALUNG Good	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Pedersen, 2009[122] DLCST Good	Yes	Yes	Yes	Low	Unclear	Yes	Yes	Yes	Low

Appendix D Table 9. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 1

First Author, Year Study Name Quality Rating	Was a consecutive or random sample of patients used?	Was a case control design avoided?	Did the study avoid inappropriate exclusions?	Bias due to patient selection?	Were the test and reference standard results interpreted independently (blinded)?	If a threshold was used, was it pre-specified?	Were the tests adequately described (or referenced)?	Were methods for calculating accuracy clearly reported and valid?	Bias due to index test (LDCT)?
Pinsky, 2015[100] NLST Fair	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Pinsky, 2015[64] NLST Good	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Pinsky, 2015[101] NLST Fair	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Pinsky, 2015[102] NLST Fair	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Scholten, 2013[103] NA Good	Yes	Yes	Yes	Low	Unclear	Yes	Yes	Yes	Low
Sverzellati, 2016[82] MILD Fair	Yes	Yes	Yes	Low	NR	Yes	Yes	No	Unclear
Swensen, 2005[130] NA Fair	Yes	Yes	Yes	Low	Unclear	Yes	Yes	Yes	Low
Tammemagi, 2017[115] PanCan Fair	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Toyoda, 2008[126] NA Fair	Yes	Yes	Yes	Unclear	Unclear	Yes	NR	Yes	Unclear
Tsushima, 2008[123] NA Fair	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Low

Appendix D Table 9. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 1

First Author, Year Study Name Quality Rating	Was a consecutive or random sample of patients used?	Was a case control design avoided?	Did the study avoid inappropriate exclusions?	Bias due to patient selection?	Were the test and reference standard results interpreted independently (blinded)?	If a threshold was used, was it pre-specified?	Were the tests adequately described (or referenced)?	Were methods for calculating accuracy clearly reported and valid?	Bias due to index test (LDCT)?
van Klaveren, 2009[120] NELSON Good	Yes	Yes	Yes	Low	Unclear	Yes	Yes	Yes	Low
Van Riel, 2015[113] NELSON Good	Yes	NA	NA	Unclear	Yes	NA	Yes	Yes	Low
Veronesi, 2008[124] COSMOS Fair	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Low
Veronesi, 2008[127] COSMOS Fair	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Low
Wagnetz, 2012[118] NA Fair	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Low
Walter, 2016[78] NELSON Good	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Wang, 2012[112] NELSON Fair	Yes	Yes	No	High	Yes	Yes	Yes	Yes	Low
Wille, 2014[108] DLCST Fair	Yes	Yes	Yes	Low	Yes	Yes	Yes	NA	Low
Xu, 2006[79] NELSON Fair	Yes	Yes	Yes	Low	Unclear	Yes	Yes	Yes	Low
Yankelevitz, 2015[105] I-ELCAP Fair	Unknown	Yes	Yes	Unclear	Yes	Yes	Yes	NA	Low

Appendix D Table 9. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 1

First Author, Year Study Name Quality Rating	Was a consecutive or random sample of patients used?	Was a case control design avoided?	Did the study avoid inappropriate exclusions?	Bias due to patient selection?	Were the test and reference standard results interpreted independently (blinded)?	If a threshold was used, was it pre-specified?	Were the tests adequately described (or referenced)?	Were methods for calculating accuracy clearly reported and valid?	Bias due to index test (LDCT)?
Yip, 2014[104] NLST, I-ELCAP Fair	Yes	Yes	No	Unclear	Yes	Yes	Yes	NA	Low
Yousaf-Khan, 2017[389] NELSON Poor	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
Zhao, 2011[77] NELSON Fair	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low
Zhao, 2014[109] NELSON Fair	Yes	Yes	Yes	Low	Yes	Yes	Yes	Yes	Low

Abbreviations: BCCA=British Columbia Cancer Agency; DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology Trial; DLCST=Danish Lung Cancer Screening Trial; I-ELCAP=International Early Lung Cancer Action Project; ITALUNG=The Italian Lung Study; KQ=Key Question; LCSDP=Lung Cancer Screening Demonstration Project; LDCT=Low-Dose Computed Tomography; LUSI=German Lung Cancer Screening Intervention Trial; MILD=Multicentric Italian Lung Detection Trial; NA=not applicable; NELSON=Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST=National Lung Screening Trial; NR=Not reported; PanCan=Pan-Canadian Early Detection of Lung Cancer Study; UKLS=UK Lung Cancer Screening Trial.

Appendix D Table 10. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 2

First Author, Year Study Name Quality Rating	Reference Standard Used	Comments about Reference Standard	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test (blinded)?	Did patients receive the reference test regardless of screening test results?	Bias due to reference standard?
Aberle, 2011[32] NLST Good	Subsequent diagnosis of LC within 1 yr	Lung cancer diagnosis was ascertained from patient questionnaires, certified by medical record abstraction, augmented by search from the NDI	Yes	Yes	Yes	Low
Aberle, 2011[58] NLST Good	Subsequent diagnosis of LC within 1 yr	Lung cancer diagnosis was ascertained from patient questionnaires, certified by medical record abstraction, augmented by search from the NDI	Yes	Yes	No	Low
Becker, 2012[60] LUSI Good	Subsequent diagnosis of LC within 1 yr	No comments	Yes	NR	Yes	Low
Becker, 2015[59] LUSI Good	Subsequent diagnosis of LC within 1 yr	No comments	Yes	NR	Yes	Low
Chung, 2017[132] NLST Good	Subsequent diagnosis of LC within 1 yr	Lung cancer diagnosis was ascertained from patient questionnaires, certified by medical record abstraction, augmented by search from the NDI	Yes	Yes	Yes	Low
Church, 2013[57] NLST Good	Subsequent diagnosis of LC within 1 yr	Lung cancer diagnosis was ascertained from patient questionnaires, certified by medical record abstraction, augmented by search from the NDI	Yes	Yes	No	Low
Croswell, 2010[119] NA Fair	Multiple	Biopsy/surgical	Yes	Unclear	No	Low
Crucitti, 2015[111] “Un repiro per la vita” Fair/Poor	Multiple	Multiple; they had protocol for workup of initial positive screen (most went on to additional imaging, some had biopsies). For sensitivity (false negatives), the reference standard is unclear and they were not really aiming to determine sensitivity	Yes, for false-positive screens/ specificity Unclear, for sensitivity	No	No	Low for false-positive screens High for sensitivity/false-negative screens
De Koning, 2020[76]	Multiple	Subsequent imaging and evaluation, diagnosis of lung cancer, registry determined lung cancer death	Yes	Yes	No	Low
Field, 2016[97] UKLS Fair	Biopsy	Diagnosis appeared to be made by lung resection or biopsy, 1 was made radiographically	Yes	Unclear	No	Low

Appendix D Table 10. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 2

First Author, Year Study Name Quality Rating	Reference Standard Used	Comments about Reference Standard	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test (blinded)?	Did patients receive the reference test regardless of screening test results?	Bias due to reference standard?
Field, 2016[117] UKLS Fair	Other	Lung cancer diagnosis ascertained from biopsy and search of the following databases: the Office for National Statistics the Hospital Episode Statistics database and the National Cancer Registration Service. However, timing of followup to determine lung cancer is unclear and authors are clear that lung cancer incidence will only be studied after data is pooled with other European studies.	Yes	Yes	Yes	Low
Gierada, 2017[110] NLST Fair	Subsequent diagnosis of LC within 1 yr	Prior reading of same LDCT scan along with clinical knowledge of progression to lung cancer	Yes	Yes	Yes	Unclear
Gohagan, 2004[70] LSS Fair	Multiple	No algorithm for this protocol; abstracted histology	Yes	Unclear	No	Low
Henschke, 2004[131] I-ELCAP Fair	Biopsy	No comments	Yes	Unclear	No	Low
Henschke, 2006[128] I-ELCAP Fair	Biopsy	No comments	Yes	Unclear	No	Low
Henschke, 2006[129] I-ELCAP Fair	Multiple	Biopsy/surgical resection	Yes	Unclear	No	Low
Henschke, 2013[107] I-ELCAP Fair	Subsequent diagnosis of LC within 1 yr	No comments	Yes	Unclear	Unclear	Unclear
Henschke, 2016[106] I-ELCAP Fair	Biopsy	Diagnosis defined on cytology from nonsurgical biopsy and path from resection	Unclear	No	Yes	Unclear

Appendix D Table 10. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 2

First Author, Year Study Name Quality Rating	Reference Standard Used	Comments about Reference Standard	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test (blinded)?	Did patients receive the reference test regardless of screening test results?	Bias due to reference standard?
Heuvelmans, 2015[325] NELSON Poor	Other	Histology was the reference	Yes	Unclear	No	High
Heuvelmans, 2013[114] NELSON Fair	Biopsy	Median followup was 4.4 yrs	Yes	Yes	No	Low
Horeweg, 2013[98] NELSON Fair	Other	Histology	Yes	Unclear	No	Unclear
Horeweg, 2014[33] NELSON Fair	Biopsy	No comments	Yes	Unclear	No	High
Infante, 2009[71] DANTE Fair	Biopsy	No comments	Yes	Unclear	No	Low
Infante, 2015[61] DANTE Fair	Other	Reference standard was histology	Yes	Unclear	No	Unclear
Kinsinger, 2017[38] LCSDP Fair	Multiple	Reference standard is LC diagnosis made by clinical teams, date are extracted from VA system central data system and probably other sources since these screened patients were tracked in a registry	Yes	No	Yes	Low
Lopes Penga, 2009[125] ITALUNG Fair	Biopsy	No comments	Yes	Unclear	No	Low
McKee, 2015[395] NA Poor	Subsequent diagnosis of LC within 1 yr	1) Diagnosed lung cancer=biopsy proven + positive PET for patients that could not undergo biopsy 2) Biopsy-prove lung cancer	Yes	No	No	Unclear
McWilliams, 2013[116] PanCan, BCCA Fair	Biopsy	1) Histopathological exam of resected surgical specimens 2) Cytopathology from needle-aspiration biopsy samples	Yes	No	No	Unclear

Appendix D Table 10. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 2

First Author, Year Study Name Quality Rating	Reference Standard Used	Comments about Reference Standard	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test (blinded)?	Did patients receive the reference test regardless of screening test results?	Bias due to reference standard?
Menezes, 2010[121] NA Fair	Biopsy	No comments	Yes	Unclear	No	Low
Paci, 2017[62] ITALUNG Good	Multiple	Biopsy reports, telephone followup, death registry	Yes	Yes	Yes	Low
Pedersen, 2009[122] DLCST Good	Biopsy	No comments	Yes	Unclear	No	Low
Pinsky, 2015[100] NLST Fair	Subsequent diagnosis of LC within 1 yr	No comments	Yes	Yes	Yes	Low
Pinsky, 2015[64] NLST Good	Subsequent diagnosis of LC within 1 yr	No comments	Yes	Yes	Yes	Low
Pinsky, 2015[101] NLST Fair	Subsequent diagnosis of LC within 1 yr	No comments	Yes	Unclear	Yes	Low
Pinsky, 2015[102] NLST Fair	Subsequent diagnosis of LC within 1 yr	No comments	Yes	Unclear	Yes	Low
Scholten, 2013[103] NA Good	Biopsy	No comments	Yes	Unclear	No	Low
Sverzellati, 2016[82] MILD Fair	Subsequent diagnosis of LC within 1 yr	No comments	Yes	Unclear	Unclear	Unclear
Swensen, 2005[130] NA Fair	Multiple	Determined by an individual's provider	Unclear	Unclear	No	High

Appendix D Table 10. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 2

First Author, Year Study Name Quality Rating	Reference Standard Used	Comments about Reference Standard	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test (blinded)?	Did patients receive the reference test regardless of screening test results?	Bias due to reference standard?
Tammemagi, 2017[115] PanCan Fair	Subsequent diagnosis of LC within 2 yrs	Any of the following 1) histopathological exam of resected surgical specimens 2) cytopathology from FNA 3) nodules stable, nodules not visible, benign calcification developed	Yes	No	No	Low
Toyoda, 2008[126] NA Fair	Other	Histology used, but procedures unclear	Yes	Unclear	No	Low
Tsushima, 2008[123] NA Fair	Multiple	Biopsy/surgical	Yes	Unclear	No	Low
van Klaveren, 2009[120] NELSON Good	Biopsy	No comments	Yes	Unclear	No	Low
Van Riel, 2015[113] NELSON Good	Other	This is study only looked at inter observer agreement, and its potential effect on subsequent testing. As such there was no clear reference standard in sensitivity and specificity were not calculated. In other words, this was the study of reliability.	NA	NA	NA	Unclear
Veronesi, 2008[124] COSMOS Fair	Biopsy	No comments	Yes	Unclear	No	Low
Veronesi, 2008[127] COSMOS Fair	Biopsy	No comments	Yes	Unclear	No	Low
Wagnetz, 2012[118] NA Fair	Multiple	Biopsy/VATS	Yes	Unclear	No	Low
Walter, 2016[78] NELSON Good	Multiple	LC diagnosis based on histology; benignity based on histology or stable size for at least 2 yrs	Yes	Unclear	Yes	Low

Appendix D Table 10. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 2

First Author, Year Study Name Quality Rating	Reference Standard Used	Comments about Reference Standard	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test (blinded)?	Did patients receive the reference test regardless of screening test results?	Bias due to reference standard?
Wang, 2012[112] NELSON Fair	Multiple	Pathology or no cancers diagnosed in 2 yr followup	Yes	No	No	Unclear
Wille, 2014[108] DLCST Fair	Subsequent imaging	Last annual CT scan	Unclear	Yes	Yes	Unclear
Xu, 2006[79] NELSON Fair	Multiple	Brushings, biopsy, VATS, resection	Yes	Unclear	Not planned	Low
Yankelevitz, 2015[105] I-ELCAP Fair	Biopsy	Diagnosis defined on cytology from nonsurgical biopsy and path from resection -- for nonsolid nodules, FNAs can be operator dependent and not useful (according to authors in introduction)	Yes	No	No	High
Yip, 2014[104] NLST, I-ELCAP Fair	Biopsy	Outcome is lung cancer incidence, relies on biopsy.	Yes	No	No	High
Yousaf-Khan, 2017[389] NELSON Poor	Multiple	LC diagnosis based on histology; benignity based on histology or stable size for at least 2 yrs	Yes	Yes	Yes	Low
Zhao, 2011[77] NELSON Fair	Subsequent diagnosis of LC within 1 yr	Subsequent diagnosis of LC within various time intervals, according to NELSON management protocol. Intervals could be 3 mos, 1 yr, or 2 yrs.	Yes	Yes	Unclear	Low
Zhao, 2014[109] NELSON Fair	Multiple	Nodules were classified as benign or malignant based on histologic examination or as benign based on stable volume for more than 2 yrs after baseline.	Yes	Unclear	No, but they were subject to the same multicomponent reference standard	Unclear

Abbreviations: BCCA=British Columbia Cancer Agency; DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology Trial; DLCST=Danish Lung Cancer Screening Trial; I-ELCAP=International Early Lung Cancer Action Project; ITALUNG=The Italian Lung Study; KQ=Key Question; LC=lung cancer; LCSDP=Lung Cancer Screening Demonstration Project; LUSI=German Lung Cancer Screening Intervention Trial; MILD=Multicentric Italian Lung Detection Trial; NA=not applicable; NDI=National Death Index; NELSON=Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST=National Lung Screening Trial; NR=Not reported; PanCan=Pan-Canadian Early Detection of Lung Cancer Study; UKLS=UK Lung Cancer Screening Trial.

Appendix D Table 11. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 3

First Author, Year Study Name Quality Rating	Is the time period between the test and reference test short enough ?	Did the whole or a random selection of the patients receive the reference test?	Did patients receive the same reference standard for the outcome specified?	Did the study have high attrition raising concern for bias?	Was an appropriate method used to handle missing data?	Bias due to flow and timing?	Quality Rating	Comments any Study With Poor Quality
Aberle, 2011[32] NLST Good	Yes	Only patients with positive screen underwent diagnostic evaluation, but all received questionnaire and NDI search	Yes	No	Yes	Low	Good	NA
Aberle, 2011[58] NLST Good	Yes	Only patients with positive screen underwent diagnostic evaluation, but all received questionnaire and NDI Search	Yes	No	Yes	Low	Good	NA
Becker, 2012[60] LUSI Good	Yes	Whole sample - LC diagnosis by biopsy or followup	Yes	No	NR	Low	Good	NA
Becker, 2015[59] LUSI Good	Yes	Whole sample - LC diagnosis by biopsy or followup	Yes	No	Yes	Low	Good	NA
Chung, 2017[132] NLST Good	Yes	Only patients with positive screen underwent diagnostic evaluation, but all received questionnaire and NDI Search	Yes	No	Yes	Low	Good	NA

Appendix D Table 11. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 3

First Author, Year Study Name Quality Rating	Is the time period between the test and reference test short enough ?	Did the whole or a random selection of the patients receive the reference test?	Did patients receive the same reference standard for the outcome specified?	Did the study have high attrition raising concern for bias?	Was an appropriate method used to handle missing data?	Bias due to flow and timing?	Quality Rating	Comments any Study With Poor Quality
Church, 2013[57] NLST Good	Yes	Only patients with positive screen underwent diagnostic evaluation, but all received questionnaire and NDI Search	Yes	No	Yes	Low	Good	NA
Croswell, 2010[119] NA Fair	Yes	No	Yes	Yes	NR	High	Fair	NA
Crucitti, 2015[111] "Un repiro per la vita" Fair/Poor	Yes, for specificity and false-positive screens; Unclear, for sensitivity	No	No	No	NR	Low for false-positive screens High for sensitivity/ false-negative screens	Fair for false-positive screens Poor for sensitivity and false-negative screens	Poor quality rating for sensitivity and false- negative outcomes is due to high risk of ascertainment bias; unreported length of followup or ascertainment approach (e.g., medical record review or endpoint verification); number of patients lost to followup; and methods of handling missing data
De Koning, 2020[76]	Yes	Yes	Yes	No	Yes	Low	Fair	NA
Field, 2016[97] UKLS Fair	Unclear how long after LDCT patients had biopsy	No	No	No	Unclear	Unclear	Fair	NA
Field, 2016[117] UKLS Fair	Unclear	Yes , if composite reference test of biopsy/imaging	Yes	No	NR (but unlikely)	Low	Fair	NA
Gierada, 2017[110] NLST Fair	No - it is possible that interval cancer developed	Yes	No	No	NA	Low	Fair	NA

Appendix D Table 11. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 3

First Author, Year Study Name Quality Rating	Is the time period between the test and reference test short enough ?	Did the whole or a random selection of the patients receive the reference test?	Did patients receive the same reference standard for the outcome specified?	Did the study have high attrition raising concern for bias?	Was an appropriate method used to handle missing data?	Bias due to flow and timing?	Quality Rating	Comments any Study With Poor Quality
Gohagan, 2004[70] LSS Fair	Unclear	No	Unclear	No	NR	Low	Fair	NA
Henschke, 2004[131] I-ELCAP Fair	Yes	No	Yes	No	NR	Low	Fair	NA
Henschke, 2006[128] I-ELCAP Fair	Yes	No	Yes	Yes (>10%)	NR	Low	Fair	NA
Henschke, 2006[129] I-ELCAP Fair	Yes	No	Yes	No	NR	Low	Fair	NA
Henschke, 2013[107] I-ELCAP Fair	Yes	Unclear	No	Unclear	Unclear	Unclear	Fair	NA
Henschke, 2016[106] I-ELCAP Fair	Yes	Selection	Yes	NR	NR	Unclear	Fair	NA
Heuvelmans, 2015[325] NELSON Poor	Unclear	No	Yes	No	Unclear	High	Poor	Poor quality rating is due to several unclear and high categories, including unclear independence of test and reference standard interpretation, unclear bias due to index test
Heuvelmans, 2013[114] NELSON Fair	NA	No	Yes	No	NA	Low	Fair	NA

Appendix D Table 11. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 3

First Author, Year Study Name Quality Rating	Is the time period between the test and reference test short enough ?	Did the whole or a random selection of the patients receive the reference test?	Did patients receive the same reference standard for the outcome specified?	Did the study have high attrition raising concern for bias?	Was an appropriate method used to handle missing data?	Bias due to flow and timing?	Quality Rating	Comments any Study With Poor Quality
Horeweg, 2013[98] NELSON Fair	Unclear	No	Yes	No	Yes	Low	Fair	NA
Horeweg, 2014[33] NELSON Fair	Unclear	No	Yes	No	Yes	Low	Fair	NA
Infante, 2009[71] DANTE Fair	Yes	No	Yes	No	NR	Low	Fair	NA
Infante, 2015[61] DANTE Fair	Unclear	No	Yes	No	Unclear	Unclear	Fair	NA
Kinsinger, 2017[38] LCSDP Fair	NR	Yes	Yes	NR	NR	Unclear	Fair	NA
Lopes Penga, 2009[125] ITALUNG Fair	Yes	No	Yes	Yes	NR	Low	Fair	NA
McKee, 2015[395] NA Poor	Yes	Yes	Yes	Yes	Unclear	High	Poor	Poor rating is due to the lack of clinical followup and inclusion of 26% of the sample in analysis. Given the small number of cases reclassified, results could change if data from missing participants had been available.
McWilliams, 2013[116] PanCan, BCCA Fair	Unclear	Biopsy	Yes	No	Yes	Unclear	Fair	NA

Appendix D Table 11. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 3

First Author, Year Study Name Quality Rating	Is the time period between the test and reference test short enough ?	Did the whole or a random selection of the patients receive the reference test?	Did patients receive the same reference standard for the outcome specified?	Did the study have high attrition raising concern for bias?	Was an appropriate method used to handle missing data?	Bias due to flow and timing?	Quality Rating	Comments any Study With Poor Quality
Menezes, 2010[121] NA Fair	Yes	No	Yes	Yes	NR	Unclear	Fair	NA
Paci, 2017[62] ITALUNG Good	Yes	All received the same outcome assessment process	Not all received biopsy	No	Yes	Low	Good	NA
Pedersen, 2009[122] DLCST Good	Yes	No	Yes	No	NR	Low	Good	NA
Pinsky, 2015[100] NLST Fair	Yes	All received the same outcome assessment process	Not all received biopsy	No	Yes	Low	Fair	NA
Pinsky, 2015[64] NLST Good	Yes	All received the same outcome assessment process	Not all received biopsy	No	Yes	Low	Good	NA
Pinsky, 2015[101] NLST Fair	Yes	All received the same outcome assessment process	Not all received biopsy	No	Yes	Low	Fair	NA
Pinsky, 2015[102] NLST Fair	Yes	All received the same outcome assessment process	Not all received biopsy	No	Yes	Low	Fair	NA
Scholten, 2013[103] NA Good	Yes	No	Yes	No	NR	Low	Good	NA
Sverzellati, 2016[82] MILD Fair	Yes	Unclear	Not all received biopsy	Unclear	Unclear	Unclear	Fair	NA

Appendix D Table 11. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 3

First Author, Year Study Name Quality Rating	Is the time period between the test and reference test short enough ?	Did the whole or a random selection of the patients receive the reference test?	Did patients receive the same reference standard for the outcome specified?	Did the study have high attrition raising concern for bias?	Was an appropriate method used to handle missing data?	Bias due to flow and timing?	Quality Rating	Comments any Study With Poor Quality
Swensen, 2005[130] NA Fair	Yes	No	Yes	Yes, for fourth annual (20%)	NR	High	Fair	NA
Tammemagi, 2017[115] PanCan Fair	Yes	Yes - if composite reference test of biopsy/imaging.	Yes	Yes	Unclear	High	Fair	NA
Toyoda, 2008[126] NA Fair	Yes	No	Yes	No	NR	Low	Fair	NA
Tsushima, 2008[123] NA Fair	Yes	No	Yes	No	NR	Low	Fair	NA
van Klaveren, 2009[120] NELSON Good	Yes	No	Yes	No	NR	Low	Good	NA
Van Riel, 2015[113] NELSON Good	NA	NA	NA	NA	NA	Low	Good	NA
Veronesi, 2008[124] COSMOS Fair	Yes	No	Yes	No	NR	Low	Fair	NA
Veronesi, 2008[127] COSMOS Fair	Yes	No	Yes	No	NR	Low	Fair	NA
Wagnetz, 2012[118] NA Fair	Yes	No	Yes	No	NR	Low	Fair	NA

Appendix D Table 11. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 3

First Author, Year Study Name Quality Rating	Is the time period between the test and reference test short enough ?	Did the whole or a random selection of the patients receive the reference test?	Did patients receive the same reference standard for the outcome specified?	Did the study have high attrition raising concern for bias?	Was an appropriate method used to handle missing data?	Bias due to flow and timing?	Quality Rating	Comments any Study With Poor Quality
Walter, 2016[78] NELSON Good	Yes	Yes	Same protocol for all	No	NA	Low	Good	NA
Wang, 2012[112] NELSON Fair	Yes	All	Yes	NR	NR	Unclear	Fair	NA
Wille, 2014[108] DLCST Fair	Yes	Intervention arm	Yes	No	NR	Low	Fair	NA
Xu, 2006[79] NELSON Fair	NR	Not planned	Likely planned, but unclear	No data	No data	Unclear	Fair	NA
Yankelevitz, 2015[105] I-ELCAP Fair	Yes	Selection	Yes	For the sample of nonsolid lesions, none.	NR	Unclear	Fair	NA
Yip, 2014[104] NLST, I-ELCAP Fair	Yes	Selection	Yes	No	Yes	Low	Fair	NA
Yousaf-Khan, 2017[389] NELSON Poor	Yes	Yes	Same protocol for all	Yes	None	High	Poor	Poor quality assessment is due to a number of unclear bias ratings, including the length of time (2 yrs) between index and reference test, and the participation rate (which was optional in the fourth round of screening).
Zhao, 2011[77] NELSON Fair	Yes	All received the same outcome assessment process	Not all received biopsy	Unclear based on this paper	Unclear	Unclear	Fair	NA

Appendix D Table 11. Risk of Bias and Overall Quality Assessment Ratings for Accuracy (KQ 3) Studies: Part 3

First Author, Year Study Name Quality Rating	Is the time period between the test and reference test short enough ?	Did the whole or a random selection of the patients receive the reference test?	Did patients receive the same reference standard for the outcome specified?	Did the study have high attrition raising concern for bias?	Was an appropriate method used to handle missing data?	Bias due to flow and timing?	Quality Rating	Comments any Study With Poor Quality
Zhao, 2014[109] NELSON Fair	Unclear	No	No	Unclear	Unclear	Unclear	Fair	NA

Abbreviations: BCCA=British Columbia Cancer Agency; DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology Trial; DLCST=Danish Lung Cancer Screening Trial; I-ELCAP=International Early Lung Cancer Action Project; ITALUNG=The Italian Lung Study; KQ=key question; LC=lung cancer; LCSDP=Lung Cancer Screening Demonstration Project; LUSI=German Lung Cancer Screening Intervention Trial; MILD=Multicentric Italian Lung Detection Trial; NA=not applicable; NDI=National Death Index; NELSON=Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST=National Lung Screening Trial; NR=not reported; PanCan=Pan-Canadian Early Detection of Lung Cancer Study; UKLS=UK Lung Cancer Screening Trial.

Appendix E Table 1. Screening Details of Included Trials, KQ 1

Trial	Inclusion Criteria	Exclusion Criteria	Description of Screening Method	Positive Screen and Evaluation Strategy
DANTE[61]	Male ages 60-74 who are current or former smokers, of at least 20 pack-years who quit less than 10 years ago	Severe comorbid conditions, life expectancy of less than 5 years, inability to comply with followup protocol, history of a previous malignancy within 10 years prior to enrollment in study	LDCT, contiguous 5 mm increments and 1.25 pitch with high-resolution bone algorithm (width 1700, level -600). Single-slice scanner with low-dose setting (140 kvp, 40 mA)	Noncalcified pulmonary nodules, hilar masses, FGG lesions, major atelectasis, endobronchial lesions, mediastinal adenopathy, pleural effusion, or pleural masses. Solid lesions, smooth and 10 mm or less: LDCT at 3, 6, and 12 months. If no change, followup 1 year. Solid lesions, nonsmooth and 5 mm or less: LDCT at 3-6 and 12 months. If no change, followup 1 year. Solid lesions, 6 mm to <10 mm: Commonly oral antibiotics. New HRCT after 6-8 weeks. Solid lesions, 10 mm to 20 mm: Oral antibiotics and new HRCT after 6-8 weeks. If no regression, PET-scan. If PET positive, tissue dx. PET-negative, close followup. Solid lesions, 20 mm or larger: Discretional antibiotics and repeat LDCT or contrast-enhanced CT and PET Subsolid (FGG) <10 mm: Oral antibiotics and new HRCT 6-8 weeks. If no regression, followup 6 months Subsolid (FGG) >10 mm: antibiotics and new HRCT 6-8 weeks. If no regression, evaluate case by case
DLCST[67]	Adult ages 50-70 who are current or former smokers with at least 20 pack-years of smoking. Former smokers should have quit after age 50 and abstinent for <10 years. Ability to climb 2 flights of stairs without pause and lung function by spirometry FEV1 of at least 30% of predicted volume	Weight of > 130 kg, history of cancer diagnosis and treatment, lung tuberculosis, illness that could shorten life expectancy to less than 10 years, chest CT in the last year for any reason	LDCT (120 kV and 40 mA)	Nodules were classified into 5 categories: 1=nodules up to 15 mm with benign characteristics; 2=no nodules or nodules <5 mm; 3=5-15 mm without benign characteristics; 4 ≥15 mm; 5=rapid-growing nodules (>25% increase in volume). Categories 1 and 2 were considered negative screening results. Category 3 were rescanned in 3 months. Categories 4 and 5 were referred to chest physicians for diagnostic workup.

Appendix E Table 1. Screening Details of Included Trials, KQ 1

Trial	Inclusion Criteria	Exclusion Criteria	Description of Screening Method	Positive Screen and Evaluation Strategy
ITALUNG[62]	55-69 years old with a smoking history at least 20 pack-years in the last 10 years or quit within the last 10 years	History of previous cancer other than nonmelanoma skin cancer and general conditions precluding thoracic surgery	LDCT, 120 to 140 kV, 20 to 43 mAs, pitch 1-2	At least one calcified solid or part solid with solid part at least 5 mm. Noncalcified, nonsolid at least 10 mm (Management of positive screens fundamentally derived from I-ELCAP)
LUSI[59, 60, 73]	Adults ages 50-69 years with a history of at least 25 years of smoking of at least 15 cigarettes per day or at least 30 years of smoking at least 10 cigarettes per day; including ex-smokers who stopped at most 10 years ago	History of cancer in the last 5 years, medical condition preventing surgical treatment and having a serious illness that shortens life expectancy to less than 10 years	LDCT (1.6-2 mSv, 1 mm slice thickness, reconstruction interval 0.8 mm and 0.7 mm, respectively)	Early recall for repeat CT depending on largest nodule size: 6 months for 5-7 diameter nodules, 3 months for 8-10 diameter and immediate pulmonology referral for >10 mm nodule. VDT calculated for known nodules and VDT above 600 days was considered negative while VDT < 600 days was positive and subject to early recall with timing to screening depending on size of nodule
LSS[69, 75]	Men and women ages 55 to 74 years with ≥30 pack-year smoking history and quit within 10 years	History of a spiral CT exam of the lungs or thorax in the previous 24 months, history of lung cancer, current treatment for any cancer other than nonmelanoma skin cancer, removal of a portion of or an entire lung, and participation in another cancer screening trial or a cancer primary prevention trial other than a smoking cessation study.	120-140 kVp, 60 mA, scan time of one second, 5 mm collimation, pitch of 2 or equivalent (depending on the model and type of scanner), and contiguous reconstructions	Noncalcified nodules ≥4 mm and several other specific findings (even with nodules <4 mm). At the 1-year examination, any noncalcified nodule ≥4 mm was considered a positive screen, and other abnormalities could be considered suspicious for lung cancer at the discretion of the radiologist
NELSON[33, 76-79, 81]	Men and women ages 50 to 74 years who smoked >15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years; current smokers or those who quit ≤10 years ago	Moderate or severe health problems and an inability to climb 2 flights of stairs; weight >140 kg; current or past renal cancer, melanoma, or breast cancer; a diagnosis of lung cancer or treatment related to lung cancer within the past 5 years; or a chest CT scan within the past year	LDCT, using volumetric approach and volume doubling time (VDT); 80-140 kV, 40-80 mAs	Volume of solid nodule >500 mm^3; pleural-based solid nodule with a minimal diameter of >10 mm; solid component in a partial solid nodule with a volume of >500 mm^3; or an indeterminate baseline screen (e.g., solid nodule 50-500 mm^3) with VDT<400 days on 3-month repeat

Appendix E Table 1. Screening Details of Included Trials, KQ 1

Trial	Inclusion Criteria	Exclusion Criteria	Description of Screening Method	Positive Screen and Evaluation Strategy
NLST[32, 63, 74]	Ages 55-74 with 30 or more pack-year history of smoking and currently smoking or quit within the past 15 years	Previous history of lung cancer, history of chest CT within 18 months before enrollment, history of hemoptysis or unexplained weight loss of more than 15 lb in preceding year	LDCT with average effective dose of 1.5 mSv	≥1 noncalcified nodule measuring at least 4 mm in long-axis diameter, mediastinal masses, pleural disease or atelectasis of more than one segment. Interpreting radiologist judgment regarding whether results were positive on the basis of findings such as noncalcified hilar or mediastinal adenopathy, atelectasis, and pleural disease. Results and recommendations were sent to the participant and his/her health provider.

Abbreviations: CT= computed tomography; DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology trial; DLCST=Danish Lung Cancer Screening Trial; dx=diagnosis; FEV=forced expiratory volume; FGG=focal ground glass; HRCT=high-resolution computed tomography; I-ELCAP=International Early Lung Cancer Action Project; ITALUNG=The Italian Lung Study; KQ=key question; LDCT=low-dose computed tomography; LSS=The Lung Screening Study; LUSI=German Lung Cancer Screening Intervention Trial; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial; PET=positron emission tomography; VDT=volume doubling time.

Appendix E Table 2. Types and Stages of Incident Lung Cancer, KQ 1

Study	Cumulative Incidence	Type of Incident Lung Cancer	Stages of Incident Lung Cancer
DANTE[61]	LDCT: 106 (8.2%) Control: 73 (5.2%)	**LDCT** Adenocarcinoma=44 (42%) Squamous 25=(24%) Non-small cell NOS=7 (6.7%) Other=7 (6.7%) Small cell=9 (8.7%) Missing=12 (11.5%) **Control** Adenocarcinoma=19 (26%) Squamous=17 (23.6%) Non-small cell NOS=8 (11.1%) Other=6 (8.3%) Small cell=6 (8.3%) Missing=16 (22.2%)	**LDCT** Stage IA=31 (29.8%) Stage IB=16 (15.4%) Stage II=7 (6.7%) Stage IIIA=9 (8.7%) Stage IIIB=8 (7.7%) Stage IV=26 (25%) Missing=7 (6.7%) **Control** Stage IA=6 (8.3%) Stage IB=10 (13.9%) Stage II=5 (6.9%) Stage IIIA=6 (8.3%) Stage IIIB=6 (8.3%) Stage IV=33 (45.8 %) Missing=6 (8.3%)

Appendix E Table 2. Types and Stages of Incident Lung Cancer, KQ 1

Study	Cumulative Incidence	Type of Incident Lung Cancer	Stages of Incident Lung Cancer
DLSCT[67]	LDCT: 100 (4.9%) Control : 53 (2.6%)	**LDCT** Adenocarcinoma=40 (40%) Adenocarcinoma + broncho-alveolar carcinoma=17 (17%) Adenocarcinoma + squamous cell carcinoma=1 (1%) Squamous cell carcinoma =14 (14%) Broncho-alveolar carcinoma=1 (1%) Non-small cell lung cancer=14 (14%), Non-small cell lung cancer + broncho-alveolar carcinoma=0 Small cell lung cancer + non-small cell lung cancer=0 Small cell lung cancer=11 (11%) Large cell neuroendocrine carcinoma=1(1%) Carcinoid=0 Unknown histology 1 (1%) **Control:** Adenocarcinoma=18 (34%) Adenocarcinoma + broncho-alveolar carcinoma=0 Adenocarcinoma + squamous cell carcinoma=0 Broncho-alveolar carcinoma=0 Squamous cell carcinoma=9 (17%) Non-small cell lung cancer=9 (17%) Non-small cell lung cancer + broncho-alveolar carcinoma=1 (1.9%) Small cell lung cancer + non-small cell lung cancer=3 (5.7%) Small cell lung cancer=11 (21%) Large cell neuroendocrine carcinoma=0 Unknown histology=1 (1.9%)	**LDCT** Stage I=50 (50%) Stage II=4 (4%) Stage IIIA=15 (15%) Stage IIIB=8 (8%) Stage IV=23 (23%) Unknown stage=0 **Control:** Stage I=8 (15.1%) Stage II=2 (3.8%) Stage IIIA=3 (5.7%) Stage IIIB=6 (11.3%) Stage IV=32 (60.4%) Unknown stage=2 (3.8%)

Appendix E Table 2. Types and Stages of Incident Lung Cancer, KQ 1

Study	Cumulative Incidence	Type of Incident Lung Cancer	Stages of Incident Lung Cancer
ITALUNG[62]	LDCT: 67 (4.1%) Control: 71 (4.5%)	**LDCT** Adenocarcinoma=29 (43%) Squamous cell carcinoma=14 (21%) Small cell lung cancers=10 (15%) Carcinoid=2 (3%) Non-small cell carcinoma=3 (4%) Unclassified=9 (13%) **Control** Adenocarcinoma=21 (30%) Squamous cell carcinoma=17 (24%) Small cell lung cancers=11 (15%) Carcinoid=0 (0%) Non-small cell carcinoma=5 (7%) Unclassified=17 (24%)	**LDCT** Stage 1=24 (36%) Stage II=5 (7%) Stage III=9 (13%) Stage IV =24 (36%) Unknown =5 (7%) **Control** Stage 1=8 (11%) Stage II=5 (7%) Stage III=8 (11%) Stage IV=35 (49%) Unknown=15 (21%) p=0.005
LUSI[59, 60, 73]	Reported for years 0-5 LDCT: 63 (3.1%) Control: 36 (1.8%) Reported at any time, with followup to a median of 8.8 years LDCT: 85 (4.2%) Control: 67 (3.3%)	Data limited to the first 5 years (99 cancers) **LDCT:** Small cell carcinoma=5 (8%) Squamous cell=10 (16%) Adenocarcinoma=43 (68%) Large cell carcinoma=1 (2%) Carcinoid=2 (3%) Carcinoma unspecified=2 (3%) **Control** Small cell carcinoma=9 (25%) Squamous cell carcinoma=6 (17%) Adenocarcinoma=18 (50%) Large cell carcinoma=1 (3%) Carcinoid=0 (0%) Carcinoma unspecified=2 (6%)	Data provided for followup to a median of 8.8 years (152 cancers) **LDCT** Stage IA=37 (44%) Stage IB=11 (13%) Stage IIA=3 (4%) Stage IIB=4 (5%) Stage IIIA=10 (12%) Stage IIIB=2 (2%) Stage IV=17 (20%) Unknown=1 (1%) **Control** Stage IA=2 (3%) Stage IB=4 (6%) Stage IIA=5 (7%) Stage IIB=4 (6%) Stage IIIA=16 (24%) Stage IIIB=5 (7%) Stage IV=30 (45%) Unknown=1 (1%)

Appendix E Table 2. Types and Stages of Incident Lung Cancer, KQ 1

Study	Cumulative Incidence	Type of Incident Lung Cancer	Stages of Incident Lung Cancer
LSS[69]	LDCT: 40 (2.4%) Control: 20 (1.5%)	**LDCT** Adenocarcinoma=24 (60%) Squamous cell carcinoma=5 (13%) Small cell carcinoma=4 (10%) Large cell carcinoma=4 (10%) Non-small cell carcinoma NOS=3 (8%) Carcinoid tumor=NR Unknown=NR **Control** Adenocarcinoma=9 (45%) Squamous cell carcinoma=6 (30%) Small cell Carcinoma=2 (10%) Large cell carcinoma=1 (5%) Non-small cell carcinoma NOS=0 Carcinoid tumor=1 (5%) Unknown=1 (5%)	**LDCT** Stage I =19 (48%) Stage II=3 (8%) Stage III=11 (28%) Stage IV=5 (13%) Unknown=2 (5%) **Control** Stage I=8 (40%) Stage II=1 (5%) Stage III=5 (25%) Stage IV=4 (20%) Unknown=2 (10%)
NELSON[33, 76-79]	Data reported for male participants only LDCT: 344 (5.2%) Control: 304 (4.6%)	**LDCT** Adenocarcinoma=179 (52%) Squamous cell carcinoma=77 (22%) Small cell carcinoma=40 (12%) Non-small cell carcinoma NOS=16 (5%) Other=32 (9%) **Control** Adenocarcinoma=133 (44%) Squamous cell carcinoma= 94 (31%) Small cell carcinoma=46 (15%) Non-small cell carcinoma NOS=13 (4%) Other=18 (6%)	**LDCT** Stage IA=105 (31%) Stage IB=34 (10%) Stage IIA=12 (4%) Stage IIB=17 (5%) Stage IIIA=34 (10%) Stage IIIB=27 (8%) Stage IV=92 (27%) Unknown=23 (7%) **Control** Stage IA=21 (7%) Stage IB=20 (7%) Stage IIA=13 (4%) Stage IIB=17 (6%) Stage IIIA=43 (14%) Stage IIIB=34 (11%) Stage IV=139 (46%) Unknown=17 (6%)

Appendix E Table 2. Types and Stages of Incident Lung Cancer, KQ 1

Study	Cumulative Incidence	Type of Incident Lung Cancer	Stages of Incident Lung Cancer
NLST[32, 63]	Median followup of 6.5 years LDCT: 1,089 (4.1%) Control: 969 (3.6%) Post-trial followup to a median of 11.3 years LDCT: 1701 (6.4%) Control: 1681 (6.3%)	Median followup of 6.5 years **LDCT** Bronchioloalveolar carcinoma=111 (10%) Adenocarcinoma=389 (35%) Squamous cell=249 (22%) Large cell carcinoma=40 (4%) Non-small cell or other=137 (12%) Small cell carcinoma=143 (13%) Carcinoid=6 (0.5%) Unknown=34 (3%) **Control** Bronchioloalveolar carcinoma=36 (4%) Adenocarcinoma=337 (34%) Squamous cell=214 (22%) Large cell carcinoma=44 (4%) Non-small cell or other=162 (16%) Small cell carcinoma=163 (16%) Carcinoid=3 (0.3%) Unknown=34 (3%) Median followup of 11.3 years **LDCT** Bronchioloalveolar carcinoma=121 (7%) Adenocarcinoma=608 (36%) Squamous cell=416 (25%) Large cell carcinoma=56 (3%) Other non-small cell=196 (12%) Small cell carcinoma=245 (14%) Carcinoid=12 (0.7%) Unknown=47 (3%) **Control** Bronchioloalveolar carcinoma=46 (3%) Adenocarcinoma=598 (36%) Squamous cell=395 (24%) Large cell carcinoma=53 (3%) Other non-small cell=251 (15%) Small cell carcinoma=291 (17%) Carcinoid=7 (0.4%) Unknown=40 (2%)	Median followup of 6.5 years **LDCT** Stage 1A 416 (40%) Stage 1B =104 (10%) Stage IIA= 35 (3.4%) Stage IIB=38 (3.7%) Stage IIIA=99 (9.5%) Stage IIIB=122 (11.7%) Stage IV=226 (21.7%) **Control** Stage 1A=196 (21.1%) Stage 1B=93 (10%) Stage IIA=32 (3.4%) Stage IIB=42 (4.5%) Stage IIIA=109 (11.7%) Stage IIIB=122 (13.1%) Stage IV=335 (36.1%) Median followup of 11.3 years **LDCT** Stage 1A=523 (31%) Stage 1B=148 (9%) Stage IIA=91 (5%) Stage IIB=43 (3%) Stage IIIA=204 (12%) Stage IIIB=84 (5%) Stage IV=468 (28%) Occult=5 Unknown=112 (7%) **Control** Stage 1A=326 (19%) Stage 1B=134 (8%) Stage IIA=80 (5%) Stage IIB=66 (4%) Stage IIIA=216 (13%) Stage IIIB=94 (6%) Stage IV=597 (36%) Occult=4 Unknown=143 (9%)

Abbreviations: DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology trial; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=The Italian Lung Study; KQ=key question; LDCT=low-dose computed tomography; LSS=The Lung Screening Study; LUSI=German Lung Cancer Screening Intervention Trial; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial; NOS=not otherwise specified; NR=not reported.

Appendix E Table 3. Incidental Findings From KQ 4 Studies

Author, Year	Study Name	Sample Size	Incidental Findings Reported
Field, 2016[117]	UKLS	4,055	Thoracic incidental findings for which supplementary radiology report was submitted: 115 Thoracic incidental findings included: Aortic dilatation: 4 Severe aortic valve calcification: 5 Mediastinal mass: 4 Mediastinal or hilar lymphadenopathy: 6 Pneumonia: 41 Bronchiectasis: 5 Pleural thickening: 8 Smoking related interstitial lung disease: 7 Severe emphysema: 9 Interstitial fibrosing lung disease (unspecified): 6 Non-specific interstitial pneumonia: 2 Usual interstitial pneumonia: 12 Sarcoidosis: 1 Oesophageal thickening or dilatation: 2 Breast mass: 1 Lobar collapse: 2 Extrathoracic incidental findings for which supplementary radiology report was submitted: 13 Extrathoracic incidental findings included: Biliary dilatation: 1 Adrenal mass: 3 Cirrhosis: 1 Hydronephrosis: 1 Liver mass: 1 Pancreatic cysts: 1 Renal mass: 3 Splenomegaly: 1 Thyroid mass: 1

Appendix E Table 3. Incidental Findings From KQ 4 Studies

Author, Year	Study Name	Sample Size	Incidental Findings Reported
Kinsinger, 2017[38]	LCSDP	2,106	Patients with ≥1 incidental finding reported: 857 (40.7%) Total N of incidental findings: 1,044 Findings included: Abdominal abnormalities and masses: 146 (14%) Aortic dilation or aneurysm: 87 (8.3%) Infectious, inflammatory, or interstitial processes: 265 (25.4%) Thyroid nodules: 25 (2.4%) Other (including CAC and emphysema): 521 (49.9%) Patients with incidental (nonnodule) findings, by demonstration site: Site 1: 211 (47.7%) Site 2: 106 (46.5%) Site 3: 135 (63.4%) Site 4: 89 (20.0%) Site 5: 149 (60.3%) Site 6: 54 (40.0%) Site 7: 81 (31.4%) Site 8: 32 (23.0%)

Appendix E Table 3. Incidental Findings From KQ 4 Studies

Author, Year	Study Name	Sample Size	Incidental Findings Reported
Morgan, 2017[167]	NA	320	Incidental findings resulting in further evaluation: 15% Findings included: Respiratory Total respiratory: 223 (69.6%) Emphysema: 162 (50.6%) Bronchial wall thickening: 126 (39.4%) Atelectasis: 52 (16.3) Ground-glass opacity: 26 (8.1%) Bronchiectasis: 14 (4.4%) Cardiovascular: Total cardiovascular: 216 (67.5%) CAC: 182 (56.0%) Aortic calcification: 66 (20.6%) Aortic dilation: 26 (8.1%) Endocrinological Total endocrinological: 23 (7.2%) Adrenal nodule 12 (3.8%) Thyroid nodule 11 (3.4%) Gastrointestinal Total gastrointestinal: 79 (24.7%) Hiatal hernia: 30 (9.4%) Liver cyst: 22 (6.8%) Dilated esophagus: 7 (2.2%) Gallstone: 6 (1.9%) Diaphragmatic hernia: 5 (1.6%) Other: 9 (2.8%) Genitourinary Total genitourinary: 14 (4.4%) Renal cyst: 8 (2.5%) Renal stone: 4 (1.3%) Renal mass: 2 (0.6%) Other Systems Total other: 78 (24.4%) Degenerative joint disease: 74 (23.1%) Compression fracture: 3 (0.9%) Breast nodule: 1 (0.3%) Splenic lesion: 1 (0.3%)

Appendix E Table 3. Incidental Findings From KQ 4 Studies

Author, Year	Study Name	Sample Size	Incidental Findings Reported
Nguyen, 2017[166]	NLST	17,309	Extrapulmonary findings (≥1 finding): 10,166 (58.7%) Potentially significant findings: 3,398 (19.6%) Minor findings 9,152 (52.9%) Significant cardiovascular findings: 1,378 (8.0%) Significant above diaphragm: 1,255 (7.3%) Significant below diaphragm: 1,311 (7.6%) Extrapulmonary malignancies: Thyroid: 14 (0.08%, 1 malignancy for every 14 found incidentally) Adrenal: 0 (0%) Kidney: 45 (0.26%, 1:37 renal abnormalities to find a malignancy) Liver: 8 (0.05%, none had significant findings on screening)
O'Grady, 2015[169]	NLST, PLCO	195,642 (53,248 from NLST 142,394 from PLCO)	Incidental thyroid cancer findings: NLST Control: 23 Intervention: 37 PLCO Control: 130 Intervention: 104
Pinsky, 2014[64]	NLST	26,722 NLST patients from LDCT arm 19,612 in <65 age cohort 7,110 in 65+ age cohort	This study reports emphysema, significant cardiovascular abnormality, abnormalities above the diaphragm, and abnormalities below the diaphragm. However, it is NR which of those are incidental. Aggregate frequencies of reported abnormal findings on screening: <65 age cohort: 6.9% 65+ age cohort: 9.2% p <0.001

Appendix E Table 3. Incidental Findings From KQ 4 Studies

Author, Year	Study Name	Sample Size	Incidental Findings Reported
Swensen, 2002[168]	NA	1,520	Patients with nonpulmonary incidental findings of significance: 210 (14%) Findings included: Renal cell cancer: 4 Indeterminate renal mass: 33 Renal calculi: 24 Bronchial carcinoid: 2 Tracheal nodule: 7 Lobar collapse: 2 Bronchiectasis: 11 Breast cancer: 3 Breast nodule: 17 Atrial myxoma: 1 Abdominal aortic aneurysm: 51 Pericardial effusion: 9 Pleural effusion: 4 Pulmonary artery calcification: 1 Lymphoma: 2 Spine metastasis: 1 Adrenal mass: 35 Pheochromocytoma: 1 Gastric tumor: 2
Wilson, 2008[137]	PLuSS	3,642	Number of screenings due to significant incidental finding: Initial screening: 82/3,642 (2.3%) Imaging studies: 19/3,642 (0.5%) Repeat screening: 50/3,423 (1.5%)

Abbreviations: CAC=coronary artery calcification; KQ=key question; LCSDP=Lung Cancer Screening Demonstration Project; NA=not applicable; NLST=National Lung Screening Trial; NR=not reported; PLCO=Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PLuSS=Pittsburgh Lung Screening Study; UKLS=UK Lung Cancer Screening Trial.

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Allibhai, 2013[259] SBRT/SABR N=185 KQ 7 Fair	NA Canada 2004-2010 Patients with T1-2N0M0 NSCLC deemed medically inoperable by an experienced thoracic surgeon Followup, median (range) 15.2 mos Funding source University, private, other unspecified	Age, median 74.8 yrs Male, N (%) 93 (*50.3*) Race/ethnicity NR Comorbidities NR	Stage, N (%) T1: 133 (72) T2: 52 (28) TNM edition(s) NR Histology, N (%) NR Tumor diameter, mean (range) 2.2 cm (0.6 to 5.7 cm)	SBRT patients, N (%) 185 (100) SBRT dosing NR, but dosage options included 48 Gy x 4 fx, 54 to 60 Gy x 3 fx, 60 Gy x 8 fx, and 50 Gy x 10 fx, depending on tumor location and size
Arnold, 2017[199] SBRT/SABR N=75 KQ 6 Fair	NCDB U.S. 2004-2012 Patients diagnosed with c-stage I NSCLC with tumors ≤4 cm who were ≥90 years old at the time of diagnosis, had no other cancer, and had no history of radiation therapy or nonstandard therapy Followup, median (range) NR Funding source NR	Age NR Male, N (%) NR Race/ethnicity NR Charlson Comorbidity Index, N (%) NR	Stage, N (%) c-stage 1: 75 (100) TNM edition(s) NR Histology, N (%) NR Tumor size, N (%) NR	SBRT patients, N (%) 75 (100) SBRT dosing 100-200 Gy x 3-5 fx: 75 (100)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Badellino, 2017[270] SBRT/SABR N=148 KQ 7 Fair	NA Italy 2004-2014 Patients with Stage I NSCLC and contraindication to surgery after multidisciplinary evaluation; ECOG performance status ≤2; accurate staging with PET and brain CT scan; prior thoracic radiation therapy Followup, median 20.5 mos Funding source NR	Age, mean (range) SBRT 3D-CRT: 75 yrs (53 to 89 yrs) SBRT VMAT: 76 yrs (52 to 88 yrs) Male, N (%) SBRT 3D-CRT: 77 (81) SBRT VMAT: 40 (75.5) Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) Clinical T1a SBRT 3D-CRT: 78 (82.1) SBRT VMAT: 30 (56.6) Clinical T1b SBRT 3D-CRT: 17 (17.9) SBRT VMAT: 23 (43.4) TNM edition(s) NR Histology, N (%) Adenocarcinoma SBRT 3D-CRT: 19 (20) SBRT VMAT: 16 (30.2) Squamous cell carcinoma SBRT 3D-CRT: 16 (16.8) SBRT VMAT: 9 (17) Other SBRT 3D-CRT: 12 (12.7) SBRT VMAT: 4 (7.5) Unknown SBRT 3D-CRT: 48 (50.5) SBRT VMAT: 24 (45.3) Tumor diameter, mean (range) SBRT 3D-CRT: 2.5 cm (1 to 5 cm) SBRT VMAT: 3 cm (1.3 to 5 cm)	SBRT patients, N (%) 148 (100) SBRT dosing, N (%) Total dose in Gy, mean (range) SBRT 3D-CRT: 110.8 (100-120) SBRT VMAT: 110.5 (100-120) 15 Gy x 3 fx SBRT 3D-CRT: 82 (86) SBRT VMAT: 9 (16) 14 Gy x 3 fx SBRT 3D-CRT: 12 (13) SBRT VMAT: 2 (3) 11 Gy x 5 fx SBRT 3D-CRT: 1 (1) SBRT VMAT: 21 (39) 7.5 Gy x 8 fx SBRT 3D-CRT: 0 (0) SBRT VMAT: 21 (39)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Bibault, 2015[254] SBRT/SABR Total N=205 Monte Carlo N=88 Type A N=117 KQ 7 Fair	NA France 2007-2013 Inoperable patients with stage NSCLC, T1 or T2 tumors >15 mm without lymph node or distant metastasis, and performance status ≤2 treated with SBRT Followup, median (range) Monte Carlo protocol: 15 mos (3 to 40 mos) Type A algorithm: 24 mos (3 to 55 mos) Private funding (Accuray, Oscar Lambret Comprehensive Cancer Center)	Age, median (range) Monte Carlo: 70.5 yrs (46 to 87 yrs) Type A: 69 yrs (49 to 92 yrs) Male, N (%) Total: *173* (*84.4*) Monte Carlo: 72 (81.8) Type A: 101 (86.3) Race/ethnicity NR Comorbidities, N (%) <u>Respiratory failure</u> Monte Carlo: 67 (76.1) Type A: 96 (82.1)	Stage, N (%) <u>Monte Carlo</u> T1a: 36 (38.7) T1b: 31 (33.3) T2a: 24 (25.8) T2b: 2 (2.2) <u>Type A</u> T1a: 50 (42.0) T1b: 36 (30.3) T2a: 30 (25.2) T2b: 3 (2.5) TNM edition(s) NR Histology, N (%) NR Tumor diameter, median (range) 22 mm (15 to 60 mm)	SBRT patients, N (%) 205 (100) SBRT dosing 60 Gy x 3 fx: NR 60 Gy x 5 fx: NR

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Brooks, 2017[204] SBRT/SABR N=772 KQs 6, 7 Fair	NA U.S. 2004-2014 Patients with c-stage 1-2 (T1-3N0M0) NSCLC not involving the bronchial tree or blocking the airway, with or without a lung cancer history (but no evidence of previous disease), and treated with SBRT; current cancer must have been outside the previously irradiated field, if patients had received previous radiation therapy for NSCLC Followup, median Age <75 yrs: 54.6 mos Age ≥75 yrs: 55.2 mos Funding source University, other unspecified source(s)	Age, median (range) Mean (range): *73.9 yrs* (46 to 91.8 yrs) Median: NR Male, N (%) *385 (49.9)* Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) Stage T1: *642 (83.2)* Stage T2: *120 (15.5)* Stage T3 (and Stage 2 NSCLC): *10 (1.3)* TNM edition(s) 7th edition Histology, N (%) Adenocarcinoma: *405 (52.5)* Squamous cell: *268 (34.7)* Other: *19 (2.5)* NSCLC NOS: *72 (9.3)* No pathologic features: *8 (1.0)* Tumor size, mean (SD) NR	SBRT patients, N (%) 772 (100) SBRT dosing, N (%) 50 Gy x 4 fx (BED 112.5 Gy): *636 (82.4)* 70 Gy x 10 fx (BED 119 Gy): *99 (12.8)* Other (75-149.6 Gy): *37 (4.8)*

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Brunelli, 2015[181] Surgery N=1,370 KQ 6 Good	NA U.S., Italy, Spain 2000-2011 Patients with p-stage 1 NSCLC with predicted postoperative FEV1 and DLCO <30% in association with peak oxygen consumption <10 mL/(kg-x-min) and deemed in stable cardiac condition and, if unstable hemodynamic conditions were present, receiving optimized cardiologic treatment prior to complete resection (but no induction chemotherapy) Followup, median 77 mos Funding source NR	Age, mean (SD) 66.1 yrs (10.2 yrs) Male, N (%) 1,014 (74) Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) p-stage 1: 1,370 (100) Stage pT1: 533 (39) TNM edition(s) 7th edition Histology, N (%) NR Tumor size, mean (SD) NR	Surgical approach, N (%) L/Bi-L: *1,304 (95.2)* P: 66 (4.8)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Bryant, 2018[196] Surgery & SBRT/SABR N=4,069 KQs 6, 7 Fair	VA U.S. 2006-2015 Patients with biopsy-proven c-stage 1 NSCLC (i.e., T1 or T2a [<5 cm in greatest dimension], N0, M0) who were treated definitively with either first-line surgery or SBRT (BED ≥100 Gy) within 6 mos of diagnosis and received pre-treatment pulmonary function tests, but no history of prior malignancy, other active cancer at diagnosis, unknown cause of death, or missing data needed to confirm eligibility Followup, median Total: *2.3 yrs* L: 2.9 yrs SLR: 2.6 yrs SBRT: 1.5 yrs Funding source Government	Age, mean (SD) Total: 67 yrs (8.2 yrs) L: 66 yrs (7.8 yrs) SLR: 69 yrs (8.5 yrs) SBRT: 71 yrs (8.6 yrs) Male, N (%) Total: 3,905 (96) L: 2,860 (96) SLR: 608 (96) SBRT: 437 (97) White, N (%) Total: 3,433 (84) L: 2,519 (84) SLR: 535 (84) SBRT: 379 (84) Comorbidities, N (%) Smoking status <u>Current</u> Total: 2,052 (50) L: 1,522 (51) SLR: 311 (49) SBRT: 219 (49) <u>Past</u> Total: 1,805 (44) L: 1,303 (44) SLR: 285 (45) SBRT: 217 (48) <u>Never</u> Total: 124 (3) L: 100 (3) SLR: 18 (3) SBRT: 6 (1)	Stage, N (%) Clinical T status <u>T1a (<2 cm)</u> Total: 1,911 (47) L: 1,329 (45) SLR: 395 (62) SBRT: 187 (42) <u>T1b (2 to 3 cm)</u> Total: 1,193 (29) L: 849 (28) SLR: 168 (26) SBRT: 176 (39) <u>T2a (3 to 5 cm)</u> Total: 965 (24) L: 808 (27) SLR: 71 (11) SBRT: 86 (19) TNM edition(s) NR Histology, N (%) <u>Adenocarcinoma</u> Total: 2,244 (55) L: 1,699 (57) SLR: 369 (58) SBRT: 176 (39) <u>Squamous cell carcinoma</u> Total: 1,375 (34) L: 964 (32) SLR: 209 (33) SBRT: 202 (45) <u>Other/unknown</u> Total: 450 (11) L: 323 (11) SLR: 56 (9) SBRT: 71 (16)	Surgical approach, N (%) L: 2,986 (73) SLR: 634 *(15.6)* <u>SLR subtypes</u> W: 414 *(65.3)* Segmental resection (SLR subtype): 220 *(34.7)* SBRT patients, N (%) 449 (11) SBRT dosing, mean dose (SD) (range) 124 (27) (100 to 216) Gy x 1-5 daily fx

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Bryant, 2018[196] (continued)		Unknown Total: 88 (2) L: 61 (2) SLR: 20 (3) SBRT: 7 (2)	Tumor size, mean (SD) NR	
Chang, 2007[192] Surgery N=10,761 KQ 6 Fair	SEER U.S. 1988-1997 Patients with diagnostic confirmation of T1N0M0 NSCLC with tumors ≤3.0 cm, but without VPI or within 2 cm of the carina, who underwent surgical resection Followup, median NR Funding source NR	Age, median 67 yrs Age, N (%) <67 yrs: 4,936 *(45.7)* ≥67 yrs: 5,825 *(54.1)* Male, N (%) 5,441 (50.6) Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) Stage 1A: 10,761 (100) TNM edition(s) NR Histology, N (%) Adenocarcinoma: *4,520* (42) SCC: *2,690* (25) Tumor size, N (%) 0.1 to 2.0 cm: 6,161 *(57.3)* 2.1 to 2.9 cm: 4,600 *(42.7)*	Surgical approach, N (%) L: 8,527 *(79.2)* SLR: 2,234 *(20.8)*

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

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Cox, 2017[186] Surgery N=1,544 1,991 KQ 6 Fair	NCDB U.S. 2003-2006 Patients with cT1-T2N0M0 lepidic adenocarcinoma treated with lobectomy or SLR, but not induction chemotherapy, radiotherapy, local excision, or pneumonectomy Followup, median NR Funding source Government	Age, median (range) Total: NR L: 69 yrs (61.0 to 75.0 yrs) SLR: 70 yrs (62.0 to 77.0 yrs) Male, N (%) Total: *711 (35.7)* L: 572 (37.0) SLR: 139 (31.1) White, N (%) Total: *1,803 (90.6)* L: 1,391 (90.1) SLR: 412 (92.2) Charlson Comorbidity Index, N (%) Score=0, n (%) Total: *1,217 (61.1)* L: 982 (63.6) SLR: 235 (52.6) Score=1, n (%) Total: *571 (28.7)* L: 424 (27.5) SLR: 147 (32.9) Score=2, n (%) Total: *203 (10.2)* L: 138 (8.9) SLR: 65 (14.5) Score >1, n (%) Total: *774 (38.9)* L: *562* (36.4) SLR: *212* (47.4)	Stage, N (%) Clinical T1 Total: *1,403 (70.5)* L: 1,043 (67.6) SLR: 360 (80.5) Clinical T2 Total: *588 (29.5)* L: 501 (32.4) SLR: 87 (19.5)	Surgical approach, N (%) L: 1,544 (77.5) SLR: 447 (22.5)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Cox, 2017[186] (continued)			TNM edition(s) 6th edition Histology, N (%) Adenocarcinoma: 1,991 (100) Tumor diameter, median (IQR) Total: NR L: 2.4 cm (1.7 to 3.4 cm) SLR: 1.6 cm (1.1 to 2.4 cm)	

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Crabtree, 2013[265] Timmerman, 2010[272] SBRT/SABR N=55 KQ 7 Fair	RTOG 0236 Canada, U.S. 2004-2006 Medically inoperable, nonpregnant, nonlactating patients aged ≥18 with Zubrod performance status score of 0-2 and cytologically or histologically proven, NSCLC, staged as T1-T2N0M0, with no active systemic, pulmonary, or pericardial infection, no history of nonsynchronous malignancy within 2 years of study entry, radiotherapy to thorax, and no plans to receive conventional radiotherapy, chemotherapy, biological therapy, vaccine therapy, or surgery as treatment (except at disease progression) Followup, median 34.4 mos Funding source Government, academic	Age, median (range) 72 yrs (48 to 89 yrs) Age >75 yrs, N (%) 21 (38.9) Male, N (%) 21 (38) White, N (%) 51 (93) Comorbidities, N (%) NR	Stage, N (%) Stage 1A: 44 (80) Stage 1B: 11 (20) TNM edition(s) NR Histology, N (%) Squamous cell carcinoma: 17 (31) Adenocarcinoma: 19 (35) Large cell undifferentiated: 3 (5) NSCLC NOS: 16 (29) Tumor size, mean (SD) NR	SBRT patients, N (%) 55 (100) SBRT dosing, N (%) 20 Gy x 3 fx: 55 (100)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Eba, 2016[201] SBRT/SABR N=40 KQ 6 Fair	NA Japan 2002-2007 Patients with histologically or cytologically proven adenocarcinoma at c-stage IA (i.e., T1N0M0) and being operable (i.e., judged able to undergo lobectomy or larger lung resection prior to registration in the JCOG0403 OR JCOG0201 trials) Followup, median NR Funding source Government	Age, median (IQR) 79 yrs (74.5 to 83.5 yrs) Male, N (%) 20 (50) Race/ethnicity NR Comorbidities, N (%) NR	c-stage, N (%) 1A: 40 (100) TNM edition(s) 6th edition Histology, N (%) Adenocarcinoma: 40 (100) Tumor size, median (IQR) 2.4 cm (1.9 to 2.6 cm)	SBRT patients, N (%) 40 (100) SBRT dosing, N (%) 48 Gy x 4 fx: 40 (100)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Fernandez, 2012[188] Surgery N=657 KQ 6 Fair	SEER U.S. 1998-2005 Patients ≥66 with c-stage 1A NSCLC treated with SLR, but no other therapies within 1 yr before diagnosis or lymph node sampling at time of surgery Followup, median 34.1 mos Funding source NR	Age, mean (SD) 75.5 yrs (5.7 yrs) Age, N (%) 66-70 yrs: 133 (20.2) 71-75 yrs: 219 (33.3) 76-80 yrs: 177 (26.9) 81-85 yrs: 92 (14.0) 86+ yrs: 36 (5.5) Male, N (%) 305 (46.4) White, N (%) 601 (91.5) Klabunde-modified Charlson Comorbidity Scores, N (%) 0: 181 (28.1) 1: 243 (37.7) 2: 104 (16.2) 3+: 116 (18.0)	Stage, N (%) c-stage 1A: 657 (100) TNM edition(s) 6th edition Histology, N (%) Adenocarcinoma: 324 (49.3) Large cell: 24 (3.7) Squamous cell: 199 (30.3) NSCLC NOS: 110 (16.7) Tumor size, mean (SD) 17.9 mm (6.3 mm) Tumor size, N (%) ≤10 mm: 98 (14.9) 11-20 mm: 362 (55.1) 21-30 mm: 197 (30.0)	Surgical approach, N (%) W: 547 (83.3) S: 92 (14.0) SLR NOS: 18 (2.7)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Ferrero, 2015[262] SBRT/SABR N=30 KQ 7 Fair	NA Italy 2012-2013 Patients with inoperable stage 1 NSCLC diagnosis and eligible for SBRT due to medical contraindications to surgery after multidisciplinary evaluation, ECOG performance status ≤2, complete staging including 18FDG-PET and CT scan, and no prior radiation therapy to site of SBRT Followup, median 14 mos Funding source NR	Age, mean (range) 77 yrs (61 to 84 yrs) Male, N (%) 23 (76.7) Race/ethnicity NR Age-adjusted Charlson Comorbidity Index, mean (range) 6.9 (3 to 14) Age-adjusted Charlson Comorbidity Index, N (%) Score <7: 16 (53.3) Score ≥7: 14 (46.7) Comorbidities <u>Smoking status, N (%)</u> Former: 19 (63.3) Current: 8 (26.7) Never: 3 (10)	Stage, N (%) 1A: 17 (56.7) 1B: 13 (43.3) TNM edition(s) NR Histology, N (%) Adenocarcinoma: 9 (30) Squamous cell: 8 (26.7) NSCLC NOS: 4 (13.3) Unknown: 9 (30) Tumor max diameter, mean (range) 25.5 mm (12 to 55 mm)	SBRT patients, N (%) 30 (100) SBRT dosing, N (%) 45 to 54 Gy x 3 fx: 9 (30) 55 Gy x 5 fx: 11 (37) 60 Gy x 8 fx: 10 (33)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Goya, 2005[195] Surgery N=*3,965* eligible (of 6,644 analyzed) KQ 6 Fair	NA Japan 1994-2001 Patients with primary histological NSCLC (adenocarcinoma, SCC, large-cell carcinoma, and adenosquamous carcinoma) resected at time of thoracotomy in 1994 at certified teaching hospitals and with complete data Followup, median NR, but ≥5 yrs Funding source NR	Age, mean (range) NR Male, N (%) NR Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) c-stage IA: 2423 (36.5) IB: 1542 (23.2) IIA: 150 (2.3) IIB: 746 (11.2) IIIA: 1270 (19.1) IIIB 366 (5.5) IV: 147 (2.2) TNM edition(s) 5th edition Histology, N (%) NR Tumor size, mean (SD) NR	Surgical approach, N (%) NR

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Grills, 2012[256] SBRT/SABR N=483 (505 tumors) KQs 6, 7 Fair	NA U.S. 1998-2010 Patients diagnosed with c-stage IA-IIB (T1-T3 N0 M0; peripheral T3 including chest-wall invasion only) or locally recurrent (after prior wedge resection) NSCLC Followup, median; mean 1.3 yrs; 1.6 yrs William Beaumont Hospital, Royal Oak, Michigan; University of Wuerzburg, Wuerzburg, Germany; Netherlands Cancer Institute, Amsterdam, The Netherlands; Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada; and Thomas Jefferson University Hospital, Philadelphia, PA; Elekta	Age, median (range) 74 yrs (42 to 94 yrs) Male, N (%) *251* (52) Race/ethnicity NR Comorbidities NR	Clinical Stage, N (%) IA (T1N0): *318* (63) IB (T2N0): *167* (33) IIA (T3N0): *10* (2) Local recurrence: *5* (1) TNM edition(s) 6th edition Histology, N (%) Adenocarcinoma: *237* (47) Squamous cell carcinoma: *162* (32) Large cell/NOS/mixed: *111* (22) Tumor size, N (%) NR	SBRT patients, N (%) 483 (100) SBRT dosing <u>William Beaumont Hospital (N=108)</u> 12 Gy x 4 fx: 69 (*63.9*) 12 Gy x 5 fx: 34 (*31.5*) <u>Netherlands Cancer Institute (N=187)</u> 18 Gy x 3 fx: 182 (*97.3*) <u>Thomas Jefferson University (N=21)</u> 10 Gy x 5 fx: 10 (*47.6*) <u>Princess Margaret Hospital (N=129)</u> 7.5 Gy x 8 fx: 13 (*10.1*) 12 Gy x 4 fx: 59 (*45.7*) 18 Gy x 3 fx: 27 (*20.9*) 20 Gy x 3 fx: 20 (*15.5*) <u>University of Wuerzburg (N=60)</u> 12.5 Gy x 3 fx: 35 (*58.3*)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Guerrera, 2015[171] Surgery N=848 KQ 6 Fair	NA Italy 2004-2012 Consecutive patients receiving surgical resection, but no preoperative treatment regimen, for Stage 1A and 1B NSCLC of any histology except a neuroendocrine subtype Followup, mean 48 mos Funding source NR	Age, median (IQR) 67 yrs (62 to 73 yrs) >75 yrs, N (%): 135 (14) Male, N (%) 610 (72) Race/ethnicity NR Comorbidities ≥1 comorbidity, N (%) 563 (77) "Smoking habit," N (%) 727 (86)	Stage, N (%) pT status pT1a: 249 (29) pT1b: 190 (23) pT2a: 409 (48) TNM edition(s) NR Histology, N (%) Adenocarcinoma: 551 (65) Bronchioalveolar carcinoma: 25 (3) Squamous cell carcinoma: 247 (29) Large-cell carcinoma: 25 (3) Tumor size, median (IQR) 2.5 cm (1.8 to 3.5 cm)	Surgical approach, N (%) W: 85 (10) S: 81 (10) L: 651 (77) Sleeve resection: 3 (0.5) Bi-L: 12 (1) P: 16 (1.5)
Haidar, 2014[257] SBRT/SABR N=55 KQ 7 Fair	NA U.S. 2002-2012 Patients treated with SBRT for early stage lung cancer Followup, median (range) NPC: 24.2 mos (1.9 to 64.6 mos) PC: 25.8 mos (4.3 to 53.4 mos) Funding source Government	Age, mean (range) NPC: 78 yrs (63 to 89 yrs) PC: 78.2 yrs (60 to 88 yrs) Male, N (%) Total: *35* (*63.64*) NPC: 17 (74) PC: 18 (56) Race/ethnicity NR Comorbidities Smokers Total: *53* (*96.36*) NPC: 22 (96) PC: 31 (97)	Stage, N (%) NPC: T1aN0M0, IA: 11 (46) T1bN0M0, IA: 7 (29) T2aN0M0, IB: 5 (21) T2bN0M0, IIA: 0 (0) T2bN0M0, IIB: 0 (0) T3aN0M0, IIB: 1 (4) TNM edition(s) 7th edition Histology, N (%) NR Tumor size, N (%) Mean (SD) NPC: 2.5 (1.1) PC: 2.7 (1.25)	SBRT patients, N (%) 55 (100) SBRT dosing, median (range) NPC: 50 Gy (48 to 56 Gy)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Husain, 2015[239] Surgery N=112,216 KQ 7 Fair	NCDB U.S. 2003-2011 Adult patients with c-stage I NSCLC Followup, median (range) NR Funding source NR	Age, median 68 yrs Age, N (%) <65 yrs: 24,535 (34.5) 65-74.99 yrs: 27,557 (42.3) ≥75 yrs: 19,083 (23.3) Male, N (%) 33,168 (46.6) White, N (%) 63,095 (88.6) Charlson-Deyo Comorbidity Index, N (%) 0: 34,750 (48.8) 1: 26,186 (36.8) 2: 10,239 (14.4)	Clinical Stage, N (%) T1N0: 48,294 (67.9) T2N0: 22,881 (32.1) TNM edition(s) 6th or 7th editions Histology, N (%) Large cell: 2278 (3.2) Squamous cell: 20,243 (28.4) Adenocarcinoma: 43,699 (61.4) Other: 4955 (7.0) Tumor size, median 2.4 cm Tumor size, N (%) ≤2 cm: 29,851 (41.9) 2.1-3 cm: 19,919 (28.0) 3.1-5 cm: 15,749 (22.1) >5 cm: 5,006 (7.0) Unknown: 650 (0.9)	Surgical approach, N (%) L: 57,569 (80.9) SLR: 13,606 (19.1)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Jeon, 2018[268] SBRT/SABR N=53 KQ 7 Fair	NA South Korea 2006-2015 Patients with Stage 1 NSCLC tumor size <5 cm, and peripheral tumor location ≥2 cm away from bronchial tree and treated with SBRT, regardless of medical operability Followup, median 37.1 mos Funding source Government	Age, median (range) 74 yrs (54 to 87 yrs) Age, N (%) ≤75 yrs: 32 (60.3) >75 yrs: 21 (39.7) Male, N (%) 40 (75.5) Race/ethnicity NR Comorbidities, N (%) Medically inoperable (i.e., significant comorbidities): 40 (75.5)	Stage, N (%) Clinical T1: 33 *(62.3)* Clinical T2: 20 *(37.7)* TNM edition(s) NR Histology, N (%) Adenocarcinoma: 22 (41.5) Squamous cell: 24 (45.3) Others: 5 (9.4) Unproven: 2 (3.8) Maximum tumor diameter range 1.5 to 4.9 cm Maximum tumor diameter, N (%) ≤2 cm: 3 (5.7) >2 to ≤3 cm: 30 (56.6) >3 cm: 20 (37.7)	SBRT patients, N (%) 53 (100) SBRT dosing, N (%) 5 Gy x 8 fx (40 Gy): 1 (1.9) 6 Gy x 7 fx (42 Gy): 2 (3.8): 6 Gy x 8 fx (48 Gy): 1 (1.9): 7 Gy x 7 fx (49 Gy): 4 (7.6) 7 Gy x 8 fx (56 Gy): 1 (1.9) 9 Gy x 5 fx (45 Gy): 2 (3.8) 10 Gy x 5 fx (50 Gy): 10 (18.8) 11.6 Gy x 5 fx (58 Gy): 1 (1.9) 12 Gy x 4 fx (48 Gy): 10 (18.8) 15 Gy x 3 fx (45 Gy): 2 (3.8) 16 Gy x 3 fx (48 Gy): 3 (5.7) 18 Gy x 3 fx (54 Gy): 16 (30.1)
Jeppesen, 2018[203] SBRT/SABR N=136 KQs 6, 7 Fair	NA Denmark 2007-2013 Patients with histologically or cytologically proven, localized T1-2N0M0 NSCLC with a maximum tumor diameter of 5 cm Followup, median 70.1 mos Funding source Private	Age, mean (range) 72.5 yrs (49 to 90 yrs) Male, N (%) 61 (45) Race/ethnicity NR Comorbidities, N (%) <u>Charlson Comorbidity Index, N (%)</u> Score 0-1: 71 (53) Score 2-3: 38 (28) Score 4+: 26 (19) <u>Smoking history, mean/median (NR which was used) (range)</u> 41 (0-130)	Stage, N (%) NR TNM edition(s) 6th edition Histology, N (%) Adenocarcinoma: 77 (57) Squamous cell: 38 (28) Other: 21 (15) Tumor diameter, mean (range) 3.1 cm (1.2 to 5.0 cm)	SBRT patients, N (%) 136 (100) SBRT dosing, N (%) <u>Total central dose to gross tumor volume (GTV)</u> 45 Gy x 3 fx (BED 112 Gy): NR (prior to October 2008) 66 Gy x 3 fx (BED 211 Gy): NR (after October 2008) <u>Total central dose to PTV</u> 30 Gy x 3 fx (BED was NR): NR (prior to October 2008) 45 Gy x 3 fx (BED 112 Gy): NR (after October 2008)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Katoh, 2017[255] SBRT/SABR N=283 (286 tumors) KQs 6, 7 Fair	NA Japan 2000-2012 Patients diagnosed with histologically proven NSCLC and peripherally located c-stage I and IIA and treated with SBRT, but not thoracic radiation therapy for simultaneous malignant tumors within three months before or after starting SBRT Followup, median (range) 28 mos (0 to 127 mos) Japan Society for the Promotion of Science; Hokkaido University	Age, median (range) 78 yrs (52 to 90 yrs) Male, N (%) 215 (*75.6*) Race/ethnicity NR Comorbidities NR	Stage, N (%) 1a and 1b: 195 (*68.2*) 2a and 2b: 91 (*31.8*) TNM edition(s) 7th edition Histology, N (%) Adenocarcinoma: 185 (*65.4*) Squamous cell carcinoma: 80 (*28.3*) Maximum tumor diameter, median (range) 1.9 cm (0.7 to 4.0 cm)	SBRT patients, N (%) 283 (100) SBRT dosing, N (%) 40 Gy x 4 fx: 94 (32.9) 48 Gy x 4 fx: 149 (52.1) 50 Gy x 5 fx: 19 (6.6)

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Khullar, 2015[178] Surgery N= 54,350 (of 92,929 total) KQ 6 Fair	NCDB U.S. 2003-2006 Patients who underwent pulmonary resection for a first or single invasive cancer, who were treated (not with palliative care) at the reporting facility, and for whom data about laterality and survival were available Followup, median NR Funding source Government, university	Age, mean (SD) 66.0 yrs (10.3 yrs) Male, N (%) NR Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) Analytic stage 1: 54,350 (62.9) Analytic stage 2: 14,137 (16.4) Analytic stage 3: 13,830 (16.0) Analytic stage 4: 4,023 (4.7) TNM edition(s) NR Histology, N (%) NR Tumor size, mean (SD) NR	Surgical approach, N (%) W: 54,350 (100)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Khullar, 2015[189] Surgery N=28,241 KQs 6, 7 Fair	NCDB U.S. 2003-2011 Patients undergoing surgical resection, but not neoadjuvant radiation or palliative care, at the same facility providing diagnosis for preoperative clinical T1a N0 NSCLC with known laterality as their first or only lifetime cancer from 2003 to 2011 (OS measures limited to patients treated from 2003-2006) Followup, median NR Funding source Government, university	Age, mean (SD) L: 65.8 yrs (9.9 yrs) W: 68.9 yrs (9.8 yrs) S: 68.7 yrs (9.4 yrs) Male, N (%) Total: *11,382 (40.3)* L: 8001 (40.6) W: 2937 (40.3) S: 444 (36.2) White, N (%) Total: *25,136 (89.0)* L: 17,464 (89.4) W: 6570 (90.9) S: 1102 (91.1) Charlson Comorbidity Index, N (%) <u>Score of 0</u> Total: *13,366 (47.3)* L: 9849 (50.0) W: 3017 (41.4) S: 500 (40.8) <u>Score of 1</u> Total: *10,783 (38.2)* L: 7293 (37.0) W: 2976 (40.8) S: 514 (41.9) <u>Score of 2+</u> Total: *4,092 (14.5)* L: 2576 (13.1) W: 1304 (17.9) S: 212 (17.3)	Stage, N (%) c-stage T1A N0 NSCLC: 28,241 (100) TNM edition(s) NR Histology, N (%) <u>Adenocarcinoma</u> Total: *18,193 (64.4)* L: 13,097 (66.4) W: 4336 (59.4) S: 760 (62.0) <u>Squamous cell carcinomas</u> Total: *6,041 (21.4)* L: 3957 (20.1) W: 1795 (24.6) S: 289 (23.6) <u>Unknown histology</u> Total: *913 (3.2)* L: 596 (3.0) W: 278 (3.8) S: 39 (3.2) Tumor size, mean (SD) L: 1.52 cm (0.39 cm) W: 1.4 cm (0.42 cm) S: 1.46 cm (0.40 cm)	Surgical approach, N (%) L: 19,718 *(69.8)* W: 7,297 *(25.8)* S: 1,226 *(4.3)*

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Koshy, 2015[200] SBRT/SABR N=498 KQ 6 Fair	NCDB U.S. 2003-2006 Patients with histologically confirmed first primary Stage 1 NSCLC who received all or part of their first course of treatment at Commission on Cancer-accredited facilities and SBRT at a calculated BED of ≥70 Gy in 1 to 10 fx Followup, median 68 mos Funding source NR	Age, N (%) 18-59 years: *40* (8.0) 60-69 years: *91* (18.3) 70-79 years: *231* (46.4) 80+ years: *136* (27.3) Male, N (%) *219* (44.0) White, N (%) *444* (89.2) Charlson Comorbidity Index, N (%) Score=0: *327* (65.7) Score=1: *125* (25.1) Score=2+: *46* (9.2)	Stage, N (%) T1: *334* (67.1) T2: *164* (32.9) TNM edition(s) 6th edition Histology, N (%) Adenocarcinoma: *180* (36.1) NSCLC NOS: *155* (31.1) Squamous cell: *146* (29.3) Large cell: *17* (3.4) Tumor size, median (IQR) T1 tumors: 2 cm (1.6 to 2.5 cm) T2 tumors: 3.7 cm (3.2 to 4.5 cm)	SBRT patients, N (%) 498 (100) SBRT dosing 20 Gy x 3 fx: *169* (34) 12 Gy x 4 fx: *80* (16) 18 Gy x 3 fx: *50* (10) 15 Gy x 3 fx: *50* (10) 16 Gy x 3 fx: *20* (4) Other dose & fx schedules: *129* (*26*)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers **Author, Year** **Treatment Type(s)** **N Enrolled** **KQs Addressed** **Quality**	**Study Characteristics** **Study or Database Name** **Country** **Study Years** **Eligibility Criteria** **Followup** **Funding Source**	**Baseline Patient Characteristics** **Age** **Gender** **Race/Ethnicity** **Comorbidities**	**NSCLC Characteristics** **Stage** **TNM Edition(s)** **Histology** **Tumor Size**	**Treatment Characteristics** **Surgical Approach** **SBRT/SABR Dosing and Frequency**
Lakha, 2014[175] Surgery N=16,315 KQ 6 Fair	SEER U.S. 2004-2010 Patients with incident, histologically confirmed NSCLC diagnosed with tumors <7 cm, without lymph node involvement (N0) or distant metastasis (M0), who were experiencing their first and only malignancy, and who underwent lobectomy but not preoperative radiotherapy Followup, median NR Funding source NR	Age, N (%) <50 yrs: *942* (*5.8*) 50-60 yrs: *2,985* (*18.3*) >60 yrs: *12,388* (*75.9*) Male, N (%) *7,707* (*47.2*) White, N (%) *13,077* (*80.2*) Comorbidities, N (%) NR	Stage, N (%) NR TNM edition(s) 7th edition Histology, N (%) Adenocarcinoma: *9,784 (60.0*) Squamous cell carcinoma: *4,273 (26.2*) Large-cell carcinoma: *598 (3.7*) Other: *257 (1.6)* Tumor size, N (%) <2 cm: *6,048 (37.1*) 2-3 cm: *4,674 (28.6*) >3-5 cm: *4,345 (26.6*) >5-7 cm: *1,248 (7.6*)	Surgical approach, N (%) L: 16,315 (100)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Lam, 2018[202] SBRT/SABR N=4,454 KQs 6, 7 Fair	NCDB U.S. 2004-2014 Patients with T1a-1bN0M0 NSCLC tumors ≤3 cm and histology classifications of adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or NSCLC NOS (but no nodal or extrapulmonary disease) who were treated at high-volume centers without chemotherapy, immunotherapy, or hormone therapy, had available survival data, and were not lost to followup Followup, median 50.2 mos Funding source NR	Age, median (range) NR Male, N (%) NR Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) NR TNM edition(s) 7th edition Histology, N (%) NR Tumor size, mean (SD) NR	SBRT patients, N (%) 4,454 (100) SBRT dosing, N (%) NR

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Landreneau, 2014[176] Surgery N=614 KQs 6, 7 Fair	NA U.S. NR Patients with c-stage 1 NSCLC >5 cm with data available from the Lung Cancer Database of the University of Pittsburgh Followup, median 5.4 yrs Funding source Government, private (Thoracic Surgery Foundation for Research and Education)	Age, mean (SD) Total: 68.5 yrs (NR) S: 68.5 yrs (9.2 yrs) L: 68.4 yrs (9.2 yrs) Male, N (%) Total: *283 (45.4)* S: 139 *(44.6)* L: 144 *(46.2)* Race/ethnicity NR Comorbidities, N (%) <u>COPD, N (%)</u> Total: *208 (33.3)* S: 103 (33.0) L: 105 (33.7) <u>Smoking status, N (%)</u> Ever Total: *480* (92.9) S: 290 (92.9) L: 290 (92.9) Never Total: *44 (7.1)* S: 22 (7.1) L: 22 (7.1)	Stage, N (%) <u>c-stage 1A</u> Total: *487 (78.0)* S: 248 *(79.5)* L: 239 *(76.6)* <u>c-stage 1B</u> Total: *137 (22.0)* S: 64 *(20.5)* L: 73 *(23.4)* TNM edition(s) 7th edition Histology, N (%) <u>Adenocarcinoma</u> Total: *360 (57.7)* S: 177 (56.7) L: 183 (58.7) <u>Squamous cell</u> Total: *186 (29.8)* S: 89 (28.5) L: 97 (31.1) Tumor size, mean (SD) Total: 2.2 cm (NR) S: 2.2 cm (1.0 cm) L: 2.2 cm (1.1 cm)	Surgical approach, N (%) S: 312 (50) L: 312 (50)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Licht, 2013[249] Surgery N=1,513 KQ 7 Fair	Danish Lung Cancer Registry The Netherlands 2007-2011 Patients undergoing standard anatomic lobectomy for c-stage 1 NSCLC Followup, median 28 mos Funding source NR	Age, N (%) <50 yrs: 51 *(3.4)* 50-59 yrs: 257 *(17.0)* 60-69 yrs: 613 *(40.5)* 70-79 yrs: 515 *(34.0)* >80 yrs: 77 *(5.1)* Male, N (%) Total: 742 (49) VATS L: *319 (44.5)* Open L: *423 (53.1)* Race/ethnicity NR Charlson Comorbidity Index <u>Median score; mean score (95% CI)</u> VATS L: 1; 1.1 (1.0 to 1.2) Open L: 0; 1.0 (0.9 to 1.1) <u>Specific scores, n (%)</u> Score=0: 762 *(50.4)* Score=1: 343 *(22.7)* Score=2: 207 *(13.7)* Score=3: 106 *(7.0)* Score=4: 37 *(2.4)* Score=5: 28 *(1.9)* Score ≥6: 30 *(2.0)*	Stage, N (%) c-stage T1: 787 *(52.0)* c-stage T2: 726 *(48.0)* TNM edition(s) NR Histology, N (%) <u>Adenocarcinoma</u> Total: *745 (49.2)* VATS L: 390 (54.4) Open L: 355 (44.6) <u>Squamous cell</u> Total: *398 (26.3)* VATS L: 145 (20.2) Open L: 253 (31.8) <u>Adenosquamous cell</u> Total: *14 (0.9)* VATS L: 8 (1.1) Open L: 6 (0.8) <u>Mixed tumor</u> Total: *246 (16.3)* VATS L: 124 (17.3) Open L: 122 (15.3)	Surgical approach, N (%) VATS L: 71 (47) Open L: 796 (53)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Licht, 2013[249] (continued)			Bronchioloalveolar carcinoma Total: *8 (0.5)* VATS L: 5 (0.7) Open L: 3 (0.4) Large-cell carcinoma Total: *60 (4.0)* VATS L: 23 (3.2) Open L: 37 (4.6) Sarcomatoid carcinoma Total: *9 (0.6)* VATS L: 4 (0.6) Open L: 5 (0.6) Salivary gland-like carcinoma Total: *1 (0.1)* VATS L: 0 (0) Open L: 1 (0.1) Non-specified NSCLC Total: *32 (2.1)* VATS L: 18 (2.5) Open L: 14 (1.8) Tumor size, mean (SD) NR	

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Lindberg, 2015[207] SBRT/SABR N=57 KQs 6, 7 Fair	NA Sweden, Norway, Denmark 2003-2005 Patients with Stage 1 T1-2N0M0 peripherally located NSCLC with no central tumor growth adjacent to trachea, main bronchus, or esophagus who were medically inoperable or refused surgery and received SBRT at the prescribed dose of 15 Gy x 3 fx; life expectancy of ≥12 mos; Karnofsky performance score ≥70; no prior malignancy within last 5 yrs Followup, median 41.5 mos Funding source Government, private	Age, mean (range) 75.2 yrs (58.9 to 86.8 yrs) Male, N (%) 26 (46) Race/ethnicity NR Comorbidities, N (%) COPD: 37 (65)	Stage, N (%) Stage T1a: 10 (18) Stage T1b: 31 (54) Stage T2a: 16 (28) TNM edition(s) 7th edition Histology, N (%) Adenocarcinoma: 19 (33) Squamous cell: 8 (14) Large cell carcinoma: 1 (2) NSCLC NOS: 10 (18) Not analyzed: 19 (33) Tumor volume, median (range) 16 mL (1 to 51 mL) Tumor diameter, median (range) 25 mm (6 to 50 mm)	SBRT patients, N (%) 57 (100) SBRT dosing, N (%) 15 Gy x 3 fx: 57 (100)

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Louie, 2016[238] Surgery *13,598* KQ 7 Fair	STS-GTS Database (Society of Thoracic Surgeons Database) U.S. 2009-2013 Patients with c-stage 1-2 NSCLC undergoing primary lobectomy performed using VATS or robotic approach, but not converted to open procedures or combined with chemotherapy or radiation therapy, at high-volume centers Followup, median (range) NR Funding source NR	Age, median (IQR) Total: 68.0 yrs (61.0-75.0 yrs) Robotic L: 69.0 yrs (61.0-75.0 yrs) VATS L: 68.0 yrs (61.0-75.0 yrs) Male, N (%) Total: 5,857 (43.1) Robotic L: 527 (43.2) VATS L: 5,330 (43.1) Race/ethnicity NR Comorbidities COPD Total: 4,497 (33.1) Robotic L: 425 (34.8) VATS L: 4,072 (32.9) Ever smoker Total: 11,339 (83.4) Robotic L: 985 (80.7) VATS L: 10,354 (83.6) ASA risk class 1, N (%) Total: 57 (0.4) Robotic L: 7 (0.6) VATS L: 50 (0.4) ASA risk class 2, N (%) Total: 2,528 (18.6) Robotic L: 197 (16.1) VATS L: 2,331 (18.8)	Stage, N (%) cT1aN0 Total: 6,095 (44.8) Robotic L: 515 (42.2) VATS L: 5,580 (45.1) cT1bN0 Total: 3,481 (25.6) Robotic L: 328 (26.9) VATS L: 3,153 (25.5) cT2aN0 Total: 2,655 (19.5) Robotic L: 269 (22.0) VATS L: 2,386 (19.3) cT2bN0 Total: 636 (4.7) Robotic L: 51 (4.2) VATS L: 585 (4.7) cT1aN1 Total: 196 (1.4) Robotic L: 16 (1.3) VATS L: 180 (1.5) cT1bN1 Total: 196 (1.4) Robotic L: 15 (1.2) VATS L: 181 (1.5) cT2aN1 Total: 240 (1.8) Robotic L: 18 (1.5) VATS L: 222 (1.8) cT2bN1 Total: 99 (0.7) Robotic L: 8 (0.7) VATS L: 91 (0.7)	Surgical approach, N (%) Robotic L: 1,220 (*9.0*) VATS L: 12,378 (*91.0*)

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Louie, 2016[238] (continued)		ASA risk class 3, N (%) Total: 10,037 (73.8) Robotic L: 932 (76.4) VATS L: 9,105 (73.6) ASA risk class 4, N (%) Total: 969 (7.1) Robotic L: 84 (6.9) VATS L: 885 (7.1) ASA risk class 5, N (%) Total: 3 (0.0) Robotic L: 0 (0) VATS L: 3 (0.0)	TNM edition(s) NR Histology, N (%) NR Tumor size, N (%) NR	

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers **Author, Year** **Treatment Type(s)** **N Enrolled** **KQs Addressed** **Quality**	**Study Characteristics** **Study or Database Name** **Country** **Study Years** **Eligibility Criteria** **Followup** **Funding Source**	**Baseline Patient Characteristics** **Age** **Gender** **Race/Ethnicity** **Comorbidities**	**NSCLC Characteristics** **Stage** **TNM Edition(s)** **Histology** **Tumor Size**	**Treatment Characteristics** **Surgical Approach** **SBRT/SABR Dosing and Frequency**
Ma, 2017[269] SBRT/SABR N=155 patients (159 tumors) KQ 7 Fair	RPCI database U.S. 2007-2015 Patients receiving definitive single-fx or triple-fx SBRT for peripheral NSCLC, but not participating in the RTOG 0915 clinical trial Followup, median 22.2 mos Funding source Private	Age, median (IQR) Total: 76.3 yrs (70.5 to 82.3 yrs) Single-fx SBRT: 76.4 yrs (70.6 to 82.5 yrs) Triple-fx SBRT: 76.2 yrs (70.1 to 82.0 yrs) Male, N (%) Total: *77 (48.4)* Single-fx SBRT: 30 (46) Triple-fx SBRT: 47 (50) Race/ethnicity NR Comorbidities <u>Medically operable, n (%)</u> Total: *42 (26.4)* Single-fx SBRT: 21 (32) Triple-fx SBRT: 21 (22) Medical inoperable, n (%) Total: *117 (73.6)* Single-fx SBRT: 44 (68) Triple-fx SBRT: 73 (78) Smoking history <u>Median pack-years (IQR)</u>: 50 (40-75) <u><50 pack-years, n (%)</u> Total: 57 *(35.8)* Single-fx SBRT: 27 (42) Triple-fx SBRT: 30 (32)	Stage, N (%) <u>Stage 1A</u> Total: *120 (75.5)* Single-fx SBRT: 54 (83) Triple-fx SBRT: 66 (70) <u>Stage 1B</u> Total: *35 (22.0)* Single-fx SBRT: 10 (15) Triple-fx SBRT: 25 (27) <u>Stage T2a</u> Total: *24 (15.1)* Single-fx SBRT: 1 (2) Triple-fx SBRT: 1 (1) <u>Stage T2b</u> Total: *2 (1.3)* Single-fx SBRT: 0 (0) Triple-fx SBRT: 2 (2) TNM edition(s) 7th edition Histology, N (%) <u>Adenocarcinoma</u> Total: *69 (43.4)* Single-fx SBRT: 34 (52) Triple-fx SBRT: 35 (37) <u>Squamous cell</u> Total: *64 (40.3)* Single-fx SBRT: 25 (38) Triple-fx SBRT: 39 (41) <u>Other</u> Total: *6 (3.8)* Single-fx SBRT: 1 (2) Triple-fx SBRT: 5 (5)	SBRT patients, N (%) 155 (100) SBRT dosing, N (%) 30 Gy x 1 fx (median dose of 30 Gy): 65 *(40.9)* 48-60 Gy x 3 fx (median dose of 60 Gy): 94 *(59.1)*

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Ma, 2017[269] (continued)		≥50 pack-years, n (%) Total: 96 *(60.4)* Single-fx SBRT: 34 (52) Triple-fx SBRT: 62 (66) NA Total: 6 *(3.8)* Single-fx SBRT: 4 (6) Triple-fx SBRT: 2 (2)	NA Total: *20 (12.6)* Single-fx SBRT: 5 (8) Triple-fx SBRT: 15 (16) Tumor size, median (IQR) Total: 2.1 cm (1.5 to 3 cm) Single-fx SBRT: 2 cm (1.5 to 3 cm) Triple-fx SBRT: 2.2 cm (1.5 to 3 cm)	
Maeda, 2010[191] Surgery N=734 KQ 6 Fair	NA Japan 1994-2003 Patients with p-stage I NSCLC with tumors up to 3 cm in maximum dimension and who underwent complete resection, but no pre- or post-operative chemotherapy or radiotherapy Followup, median NR Funding source Government, university	Age, median (range) Age <65 yrs: 371 *(52.0)* Age ≥65 yrs: 342 *(48.0)* Male, N (%) 385 *(54)* Race/ethnicity NR Comorbidities, N (%) Smoking status Nonsmoker: 318 *(44.6)* Current or former smoker: 395 *(55.4)*	Stage, N (%) Overall with Stage 1: 605 *(84.9)* Stage 1A: *357 (50.1)* Stage 1B: *248 (34.8)* TNM edition(s) 7th edition Histology, N (%) Adenocarcinoma: 569 *(79.8)* Squamous cell carcinoma: 104 *(14.6)* Large cell carcinoma: 27 *(3.8)* Adenosquamous carcinoma: 9 *(1.3)* Pleomorphic carcinoma: 4 *(0.56)* Tumor size, N (%) ≤20 mm: 393 *(55.1)* >20 mm: 320 *(44.9)*	Surgical approach, N (%) L: 616 *(86.4)* S or W: 97 *(13.6)*

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Maeda, 2012[184] Surgery N=1,074 KQ 6 Fair	NA Japan 1992-2007 Consecutive patients receiving complete surgical resection by lobectomy or systematic lymph node dissection for c-stage 1A NSCLC adenocarcinoma Followup, median 57 mos Funding source Government, other not disclosed	Age, N (%) <65 yrs: 562 (53) >65 yrs: 508 (47) Male, N (%) 499 (47) Race/ethnicity NR Comorbidities, N (%) <u>Smoking status</u> Never: 528 *(49.3)* Ever: *543 (50.7)* <u>Smoking history</u> No pack-years: 528 *(49.3)* 0 ≤ pack-years ≤ 10: 75 *(7.0)* 10 < pack-years ≤ 20: 74 *(6.9)* 0 ≤ pack-years ≤ 20: 677 (63) 20 < pack-years ≤ 40: 182 *(17.0)* 40 < pack-years ≤ 60: 126 *(11.8)* Pack-years >60: 85 *(7.9)* Pack-years >20: 393 (37)	Stage, N (%) c-stage 1A: 1,070 (100) TNM edition(s) 7th edition Histology, N (%) Adenocarcinoma: 1,074 (100) Well-differentiated histology: 456 (43) Moderately/poorly differentiated histology: 614 (57) Tumor size, N (%) <2.0 cm (T1a): 703 (66) 2.1 to 3.0 cm (T1b): 367 (34)	Surgical approach, N (%) L: 1,074 (!00)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Mathieu, 2015[260] SBRT/SABR N=45 KQ 7 Fair	NA Canada 2010-2013 Patients with biopsy-confirmed stage 1 NSCLC (T1-T2aN0M0), Karnofsky performance status ≥60, and medical inoperability because of poor pulmonary function, medical comorbidities, or surgery refusal, but no prior thoracic radiation or cancer in last 5 yrs Followup, median 41 mos Funding source NR	Age, median (range) 77 yrs (60 to 94 yrs) Male, N (%) 17 (38) Race/ethnicity NR Comorbidities, N (%) Charlson Comorbidity Index Score=0-2: 4 (9) Score=3-4: 24 (53) Score >4: 17 (38) Smoking pack-years, median (range) 45 (0-100)	Stage, N (%) T1a: 19 (42) T1b: 17 (38) T2a: 9 (20) TNM edition(s) NR Histology, N (%) Adenocarcinoma: 25 (56) Other: 4 (9) Squamous cell: 14 (31) Large cell: 2 (4) Gross tumor volume, median (range) 7.9 mL (0.5 to 35.9 mL)	SBRT patients, N (%) 45 (100) SBRT dosing 60 Gy x 3 fx: 32 (71) 50 Gy x 4 fx: 7 (16) 50 Gy x 5 fx: 6 (13)

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Matsuo, 2014[198] SBRT/SABR N=115 KQs 6, 7 Fair	Databases maintained by Departments of Radiation Oncology & Thoracic Surgery of Kyoto University Hospital Japan 2003-2009 Consecutive patients with histological confirmation of c-Stage I NSCLC ≤50 mm who underwent SBRT because of medical comorbidities Followup, median 6.7 yrs Japan Society for the Promotion of Science	Age, median (range) 77 yrs (56 to 88 yrs) Male, N (%) 83 (72.17) Charlson Comorbidity Index score, median (range) 2 (0 to 8) Race/ethnicity NR	Stage, N (%) c-stage I: 115 (100) TNM edition(s) NR Histology, N (%) Adenocarcinoma: 58 (*50.43*) Squamous cell carcinoma: 41 (*35.65*) Large cell carcinoma: 4 (*3.48*) Others: 12 (*10.43*) Tumor diameter, median (range) 25 mm (10 mm to 45 mm)	SBRT patients, N (%) 115 (*63.89*) SBRT dosing, N (%) 48 Gy x 4 fx: *108* (*93.91*) 60 Gy x 8 fx: 5 (*4.35*) 56 Gy x 4 fx: 1 (*0.09*) 60 Gy x 4 fx: 1 (*0.09*)

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Mediratta, 2014[177] Surgery N=540 KQs 6, 7 Good	NA U.K. 2001-2012 Patients with Stage 1 adenocarcinoma or squamous carcinoma who had undergone a potentially curative wedge resection Followup, median 1,012 days Funding source NR	Age, median (IQR) 72 yrs (64 to 77 yrs) Male, N (%) *274 (51)* Race/ethnicity NR Comorbidities COPD, N (%) 114 (21) Emphysema, N (%) 21 (4) Smoking status, N (%) Current: 128 (24) Former: 305 (57) Never: 107 (19) Pack-year history, median (IQR) 25 (23.2 to 26.7)	Stage, N (%) T stage 1: 411 (76) T stage 2: 129 (24) N stage 0: 540 (100) TNM edition(s) NR Histology, N (%) Adenocarcinoma: 400 (74) Squamous carcinoma: 140 (26) Tumor diameter, median (IQR) 20.5 mm (15 to 25 mm)	Surgical approach, N (%) W: 540 (100)

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Melvan, 2015[243] Surgery N=127,366 (of 215,645 total) KQ 7 Fair	NCDB U.S. 2003-2011 Patients with one lifetime NSCLC diagnosis that underwent surgical resection, or such cases where the reported tumor was the first of multiple diagnoses Followup NR Funding source Government, university	Age, mean (SD) NR Age, N (%) NR Male, N (%) NR Race/ethnicity NR Comorbidities NR	Analytic stage, N (%)† 0 to 1: 127,366 (62.7) II: 35,679 (17.6) III: 31,090 (15.3) IV: 8,938 (4.4) Missing: 12,572 (5.83) TNM edition(s) NR Histology, N (%) NR Tumor size NR	Surgical approach, N (%) W, <1 lobe: NR S: NR L: NR P: NR

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Nagata, 2015[205] SBRT/SABR N=169 KQs 6, 7 Fair	JCOG Japan 2004-2008 Histologically or cytologically proven NSCLC (clinical T1N0M0) staged by at least bronchoscopy and CT; ECOG performance status 0 to 2; age ≥20 years; PaO2 ≥60 torr (under room air); FEV 1.0 ≥700 mL; no history of radiation therapy, chemotherapy, or continuous systemic steroid therapy; classified as either operable or inoperable by surgeons, study coordinator, and group coordinator; dose constraints of all organs at risk expected to be fulfilled; no apparent or active pneumonitis, pulmonary fibrosis, infectious disease, severe psychological disorder, or synchronous or metachronous cancer within last 5 yrs Followup, median NR Funding source Government, private (nonprofit organization)	Age, N (%) <75 yrs: *59 (34.9)* 76-80 yrs: *61 (36.1)* 81 yrs: *49 (29)* Male, N (%) *122 (72.2)* White, N (%) 0 (0) Comorbidities, N (%) Smoking history (no further details provided): *130 (76.9)*	Stage, N (%) NR TNM edition(s) 6th edition Histology, N (%) Adenocarcinoma: *90 (53.3)* Squamous cell carcinoma: *61 (36.1)* Other: *18 (10.7)* Tumor size, median (range) 21 mm (9 to 30 mm)	SBRT patients, N (%) 169 (100) SBRT dosing, N (%) Prescribed dose of 48 Gy x 4 fx: NR Planned dose constraint for lung of 40 Gy x 4 fx: NR

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Nakamura, 2015[173] Surgery N=1,336 KQ 6 Fair	NA Japan 1983-2012 Patients undergoing resection of lung cancer in the hospital Followup, mean (SD) (range) 37 mos (34 mos) (1 to 219 mos) Funding source NR	Age, N (%) <69: 553 (*54.4*) ≥69: 463 (*45.6*) Male, N (%) 640 (*63.0*) Race/ethnicity NR Comorbidities NR	Stage, N (%) (for N analyzed=1016) p-stage 1A: 402 (39.6) p-stage 1B: 220 (21.7) p-stage 2A: 92 (9.1) p-stage 2B: 71 (6.99) p-stage 3A: 192 (18.9) p-stage 3B: 10 (0.98) p-stage 4: 29 (2.9) TNM edition(s) 7th edition Histology, N (%) Adenocarcinoma: 660 (*67.0*) Nonadenocarcinoma: 356 (*35.0*) Tumor size, N (%) NR	Surgical approach, N (%) L: 1,016 (*76.0*) SLR: 174 (*13.0*) P: 106 *(8.0)* Combined resection: 40 (*3.0*)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Nyman, 2016[267] SBRT/SABR N=49 KQ 7 Fair	SPACE Norway, Sweden 2007-2011 Patients with Stage 1 T1-2N0M0 NSCLC (max tumor diameter ≤6 cm and no central tumor growth adjacent to trachea, main bronchus, or esophagus) who were medically inoperable or refused surgery and had WHO performance status score 0-2, but no prior malignancy in last 5 yrs, history of thoracic radiotherapy, or current neoadjuvant or adjuvant chemotherapy or targeted drugs Followup, median 37 mos Funding source Private	Age, mean (range) 73 yrs (57 to 86 yrs) Male, N (%) 22 (45) Race/ethnicity NR Comorbidities, N (%) COPD: 35 (71)	Stage, N (%) Clinical T1: 26 (53) Clinical T2: 23 (47) TNM edition(s) 6th edition Histology, N (%) Adenocarcinoma: 16 (33) Squamous cell: 9 (18) NSCLC NOS: 5 (10) Not performed: 18 (37) Missing: 1 (2) Tumor size, mean (SD) NR	SBRT patients, N (%) 49 (100) SBRT dosing, N (%) 66 Gy x 3 fx: 49 (100)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Okada, 2006[193] Surgery N=567 KQ 6 Fair	NA Japan 1992-2001 Patients with a clinical T1N0M0 peripheral lung tumor of 2 cm or less in every dimension, located in the outer one third of the lung on CT scan, and able to tolerate a lobectomy as evaluated by cardiopulmonary functional tests, no history of previously treated cancer Followup, median (range) Total: 72 mos (22 to 158 mos) L: 71 mos (22 to 158 mos) SLR: 72 mos (29 to 155 mos) Funding source NR	Age, mean (range) SLR: 63.2 yrs (35 to 82 yrs) L: 64.0 yrs (38 to 84 yrs) Male, N (%) *313 (55.2)* Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) c-stage T1N0M0: 567 (100) TNM edition(s) NR Histology, N (%) Adenocarcinoma: *505 (89)* SCC: *57 (10.1)* Adenosquamous: *5 (0.9)* Tumor size, mean (range) SLR: 15.7 mm (5 to 20 mm) L: 16.2 mm (8 to 20 mm) Tumor size, N (%) 0 to 10 mm: *57 (10.1)* 11 to 20 mm: *510 (89.9)* Tumor size, mean (range) SLR: 15.7 mm (5 to 20 mm) L: 16.2 mm (8 to 20 mm) Tumor size, N (%) 0 to 10 mm: *57 (10.1)* 11 to 20 mm: *510 (89.9)*	Surgical approach, N (%) Assigned L: 262 (46.2) SLR: 305 (53.8) Actual S: 230 *(40.6)* W: *32 (5.6)* L: *303 (48.9)* T: 2 *(0.4)*

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Puri, 2014[242] Surgery N=1,066 KQs 6, 7 Fair	ACOSOG z4032, z4033 U.S. 2000-2010 Patients with c-stage 1 NSCLC Followup NR Funding source NR	Age NR Male, N (%) NR Race/ethnicity NR Comorbidities NR	Stage, N (%) NR TNM edition(s) NR Histology, N (%) NR Tumor size, N (%) NR	Surgical approach, N (%) L: *782 (73.4)* SLR or other resection: *282 (26.5)* VATS approach: *328 (30.8)* Open approach: *738 (69.2)*
Puri, 2015[252] Surgery N=111,731 KQ 7 Fair	NCDB U.S. 1998-2010 Patients with c-stage I NSCLC (tumor size ≤5 cm) who received treatment with either surgical resection or SBRT, but not neoadjuvant therapy or palliative treatment Followup, mean 36.5 mos Funding source Government	Age, mean (SD) Surgical resection (full set): 67.9 yrs (9.9 yrs) SLR (full set): 70.1 yrs (9.3 yrs) Male, N (%) Surgical resection (full set): *52,393 (46.9)* SLR (full set): *11,622 (44.2)* White, N (%) Surgical resection (full set): 110,560 (90)	Stage, N (%) <u>Clinical T1</u> Surgical resection (full set): 80,184 (71.8) SLR (full set): NR <u>Clinical T2</u> Surgical resection (full set): 31,547 (28.2) SLR (full set): NR TNM edition(s) NR Histology, N (%) NR	Surgical approach, N (%) L: 82,749 *(74.1)* W: 22,010 *(19.7)* S: 4,282 *(3.8)* P: 2,690 *(2.4)*

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Puri, 2015[252] (continued)		SLR (full set): 24,016 (91.3) Charlson/Deyo Comorbidity Score, N (%) <u>Score=0</u> Surgical resection (full set): 42,761 *(50.6)* SLR (full set): 9,087 *(45.5)* <u>Score=1</u> Surgical resection (full set): 30,401 *(36)* SLR (full set): 7,662 *(38.4* <u>Score=2</u> Surgical resection (full set): 11,342 *(13.4)* SLR (full set): 3,211 *(12.2))*	Tumor size, mean (SD) Surgical resection (full set): 24.1 mm (10.7 mm) SLR (full set): 19.3 mm (9.0 mm)	
Razi, 2016[180] Surgery N=1,640 KQ 6 Fair	SEER U.S. 1998-2007 Patients aged ≥75 y who underwent lobectomy or SLR (W or S), but not chemotherapy or radiotherapy, for Stage IA (T1a/b, N0, M0) NSCLC, restricted by histology to either squamous cell or adenocarcinoma Followup, median NR Funding source NR	Age, median 78 yrs Age, mean (SE) L/Bi-L: 78.7 yrs (0.10 yrs) S: 79.4 yrs (0.35 yrs) W: 79.7 yrs (0.17 yrs) Male, N (%) L/Bi-L: *502* (47.8) S: *48* (40.3) W: *222* (47.2) White, N (%) L/Bi-L: 951 (90.5) S: 108 (90.8) W: 427 (90.9) Comorbidities, N (%) NR	Stage, N (%) c-stage 1A: 1,640 (100) TNM edition(s) 7th edition Histology, N (%) <u>Adenocarcinoma</u> L/Bi-L: 657 (62.5) S: 71 (59.7) W: 254 (54) <u>Squamous cell carcinoma</u> L/Bi-L: 394 (37.5) S: 48 (40.3) W: 216 (46)	Surgical approach, N (%) L/Bi-L: 1,051 *(64.1)* S: 119 *(7.3)* W: 470 *(28.6)*

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Razi, 2016[180] (continued)			Tumor size, mean (SE) L/Bi-L: 2.2 cm (0.02 cm) S: 1.9 cm (0.06 cm) W: 1.9 cm (0.03 cm)	
Robinson, 2013[266] SBRT/SABR N=78 KQ 7 Fair	NA U.S. 2004-2008 Patients with pathologically confirmed Stage 1 NSCLC and receiving SBRT with BED ≥100 Gy Followup, median 50.3 mos Funding source NR	Age, median (range) 76 yrs (31 to 93 yrs) Male, N (%) *44 (56.4)* White, N (%) 68 (87.2) Charlson Comorbidity Index, median (range) Raw score: 4 (2 to 10) Age-adjusted score: 7 (3 to 12) ACE-27 Comorbidity Index, median (range) 2 (0 to 3)	Clinical Stage, N (%) T1a: 36 (46.2) T1b: 20 (25.6) T2a: 19 (24.4) T2b: 3 (3.8) T3: 0 (0) TNM edition(s) 7th edition Histology, N (%) Adenocarcinoma: 36 (46.2) Squamous cell: 25 (32.1) NSCLC NOS: 16 (20.5) Other/unknown: 1 (1.3) Maximal tumor size, median (range) 2 cm (1.1 to 6 cm)	SBRT patients, N (%) 78 (100) SBRT dosing, N (%) 54 Gy x 3 fx: 68 (87.2) 50 Gy x 5 fx: 4 (5.1) 45 Gy x 3 fx: 6 (7.7)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Rosen, 2014[258] SBRT/SABR N=79 KQ 7 Fair	NA U.S. 2005-2010 Patients with biopsy-proven or clinically diagnosed T1-2N0M0 NSCLC and treated with TomoTherapy helical SBRT Followup, median 27 mos Funding source NR	Age, median (range) 73 (27 to 92) Male, N (%) 33 (42) Race/ethnicity NR Comorbidities NR	Stage, N (%) T1a: 59 (75) T1b: 20 (25) TNM edition(s) NR Histology, N (%) Adenocarcinoma: 22 (28) Squamous cell: 18 (23) NSCLC NOS: 22 (28) No histology: 17 (21) Tumor diameter, mean (range) 2.3 cm (0.5 to 6.0 cm)	SBRT patients, N (%) 79 (100) SBRT dosing, N (%) 12 Gy x 4 fx: 20 (*25.3*) 12 Gy x 5 fx: 59 (*74.7*)
Rosen, 2014[244] Surgery N=66,283 (of 119,146 total) KQ 7 Fair	NCDB U.S. 2004-2009 All patients over the age of 19 years diagnosed with NSCLC and undergoing surgical resection (W, S, L/Bi-L, extended L/Bi-L, P) Followup, median (range) NR Funding source University	Age, median (range) NR Male, N (%) NR Race/ethnicity NR Comorbidities NR	Stage, N (%) p-stage 1: 66,283 (*55.6*) p-stage 2: 17,434 (*14.6*) p-stage 3: 15,610 (*13.1*) p-stage 4: 4,196 (*3.5*) Unknown: 15,623 (*13.1*) TNM edition(s) NR Histology, N (%) NR Tumor size, N (%) NR	Surgical approach, N (%) W: NR S: NR L/Bi-L: NR Extended L/Bi-L: NR P: NR

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Rosen, 2016[185] Surgery & SBRT/SABR Total N=15,433 PSM subset N=3,562 <u>Primary analyses (i.e., patients with Charlson-Deyo score=0)</u> Total: 15,433 L (full selected set): 13,652 L (PSM subset): 1,781 SBRT: 1,781 <u>Secondary analyses (i.e., patients unselected based on Charlson-Deyo score)</u> Total: 29,267 L (unselected): 29,032 L (unselected PSM subset) 235 SBRT (unselected PSM subset): 235 KQs 6, 7 Good	NCDB U.S. 2008-2012 <u>Primary analysis</u> Patients aged >20 years, diagnosed with invasive c-stage I NSCLC and free of comorbidities (i.e., AJCC overall stage group of I, IA, or IB, and T stage of T1, T1a, T1b, or T2a, tumor size ≤5 cm, N stage of 0, and M stage of 0) and treated with lobectomy or SBRT, but not chemotherapy or radiotherapy <u>Secondary analysis</u> Patients aged >20 years diagnosed with invasive c-stage I NSCLC, as diagnosed for the primary analysis, with or without comorbidities who underwent SBRT after refusing surgery, but not chemotherapy or radiotherapy Followup, median Total: *30.1 mos* Lobectomy: 31.6 mos SBRT: 28.6 mos Funding source University	Age, median (range) <u>Primary analysis</u> Unmatched cohort <u>Mean (SD)</u> L: 66.6 (10.2) SBRT: 75.5 (9.1) Propensity-matched subset <u>Mean (SD)</u> L (PSM subset): 74.8 (7.8) SBRT: 75.5 (9.1) <u>Secondary analysis</u> Unmatched cohort <u>Mean (SD)</u> L (unselected): 66.9 (9.7) SBRT (unselected PSM subset): 75.3 (8.9) Propensity-matched subset <u>Mean (SD)</u> L (unselected PSM subset) 75.0 (8.2) SBRT (unselected PSM subset): 75.3 (8.9) Male, N (%) <u>Primary analysis</u> Unmatched cohort L: 6,111 (45) SBRT: 767 (43)	Stage, N (%) <u>Primary analysis</u> Unmatched cohort <u>Clinical T1</u> L: 9,543 (70) SBRT: 1,371 (77) <u>Clinical T2</u> L: 4,109 (30) SBRT: 410 (23) Propensity-matched subset	Surgical approach, N (%) Primary analysis <u>Unmatched cohort</u> L: 13,652 *(88.5)* <u>Propensity-matched subset</u> L: 1,781 *(50)* Secondary analysis <u>Unmatched cohort</u> L: 29,032 *(99.2)* <u>Propensity-matched subset</u> L: 235 *(0.8)* SBRT patients, N (%) Primary analysis <u>Unmatched cohort</u> 1,781 *(11.5)* <u>Propensity-matched subset</u> 1,7812 *(50)* Secondary analysis <u>Unmatched cohort</u> SBRT: 235 (100) <u>Propensity-matched subset</u> SBRT: 235 (100) SBRT dosing, N (%) 100-200 Gy x 3-5 fx: 1,781 (100)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Rosen, 2016[185] (continued)		Propensity-matched cohort L (PSM subset): 777 (44) SBRT: 767 (43) Secondary analysis Unmatched cohort L (unselected): 13,713 (47) SBRT (unselected PSM subset): 95 (40) Propensity-matched cohort L (unselected PSM subset) 84 (36) SBRT (unselected PSM subset): 95 (40) White, N (%) Primary analysis Unmatched cohort L: 11,938 (87) SBRT: 1,616 (91) Propensity-matched cohort L (PSM subset): 1,610 (90) SBRT: 1,616 (91) Secondary analysis Unmatched cohort L (unselected): 25,573 (88) SBRT (unselected PSM subset): 208 (89)	Clinical T1 L (PSM subset): 1,374 (77) SBRT: 1,371 (77) Clinical T2 L (PSM subset): 407 (23) SBRT: 410 (23) Secondary analysis Unmatched cohort	

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Rosen, 2016[185] (continued)		Propensity-matched cohort L (unselected PSM subset) 212 (90) SBRT (unselected PSM subset): 208 (89) Comorbidities, N (%) Primary analysis Charlson-Deyo score: 0 (0) for all patients in the unmatched and propensity-matched cohorts Secondary analysis, N (%) Unmatched cohort Charlson-Deyo score=0 L (unselected): 13,652 (47) SBRT (unselected PSM subset): 157 (67) Charlson-Deyo score=1 L (unselected): 10,877 (37) SBRT (unselected PSM subset): 50 (21) Charlson-Deyo score=2+ L (unselected): 4,503 (16) SBRT (unselected PSM subset): 28 (12) Propensity-matched subset Charlson-Deyo score=0 L (unselected PSM subset) 156 (66) SBRT (unselected PSM subset): 157 (67)	Clinical T1 L (unselected): 20,555 (71) SBRT (unselected PSM subset): 174 (74) Clinical T2 L (unselected): 8,477 (29) SBRT (unselected PSM subset): 61 (26) Propensity-matched cohort Clinical T1 L (unselected PSM subset) 175 (74) SBRT (unselected PSM subset): 174 (74) Clinical T2 L (unselected PSM subset) 60 (26) SBRT (unselected PSM subset): 61 (26)	

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Rosen, 2016[185] (continued)		Charlson-Deyo score=1 L (unselected PSM subset) 52 (22) SBRT (unselected PSM subset): 50 (21) Charlson-Deyo score=2+ L (unselected PSM subset) 27 (11) SBRT (unselected PSM subset): 28 (12)	TNM edition(s) 6th & 7th editions Histology, N (%) Primary analysis, N (%) Unmatched cohort Adenocarcinoma L: 9,379 (69) SBRT: 850 (48) Squamous cell carcinoma L: 3,502 (26) SBRT: 583 (33) Large cell carcinoma L: 317 (2) SBRT: 17 (1)	

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Rosen, 2016[185] (continued)			Other L: 454 (3) SBRT: 331 (19) Propensity-matched cohort Adenocarcinoma L: 886 (50) SBRT: 850 (48) Squamous cell carcinoma L: 646 (36) SBRT: 583 (33) Large cell carcinoma L: 21 (1) SBRT: 17 (1) Other L: 228 (13) SBRT: 331 (19) Secondary analysis, N (%) Unmatched cohort Adenocarcinoma L (unselected): 18,200 (63) SBRT (unselected PSM subset): 125 (53) Squamous cell carcinoma L (unselected): 9,130 (31) SBRT (unselected PSM subset): 69 (29) Large cell carcinoma L (unselected): 797 (3) SBRT (unselected PSM subset): *2 (0.9)*	

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Rosen, 2016[185] (continued)			Other L (unselected): 905 (3) SBRT (unselected PSM subset): 39 (17) Propensity-matched cohort Adenocarcinoma L (unselected PSM subset) 125 (53) SBRT (unselected PSM subset): 125 (53) Squamous cell carcinoma L (unselected PSM subset) 61 (26) SBRT (unselected PSM subset): 69 (29) Large cell carcinoma L (unselected PSM subset) *4 (1.7)* SBRT (unselected PSM subset): *2 (0.9)* Other L (unselected PSM subset) 45 (19) SBRT (unselected PSM subset): 39 (17)	

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Rosen, 2016[185] (continued)			Tumor size, mean (SD) <u>Primary analysis</u> Unmatched cohort L: 25.4 mm (10.5 mm) SBRT: 23.8 mm (9.3 mm) <u>Propensity-matched subset</u> L: 23.7 mm (10.0 mm) SBRT: 23.8 mm (9.3 mm) <u>Secondary analysis</u> <u>Unmatched cohort</u> L (unselected): 25.1 mm (10.5 mm) SBRT (unselected PSM subset): 24.0 mm (9.3 mm) <u>Propensity-matched subset</u> L (unselected PSM subset) 23.6 mm (9.9 mm) SBRT (unselected PSM subset): 24.0 mm (9.3 mm)	

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Samson, 2015[240] Surgery N=55,653 KQs 6, 7 Fair	NCDB U.S. 2000-2012 Overall and PSM samples: Patients diagnosed with c-stage I NSCLC undergoing surgical resection Single-center sample: Patients diagnosed with c-stage I NSCLC undergoing surgical resection Followup, median (range) NR Funding source Government	Age, median (range) PSM analysis Early surgery: 68.7 (9.8) Delayed surgery: 68.8 (9.7) Single-center analysis Early surgery: 66.0 (10.1) Delayed surgery: 66.9 (9.7) Male, N (%) PSM analysis Male Early surgery: 6,505 (48.1) Delayed surgery: 6,564 (48.6) Single-center analysis Female Early surgery: 276 (53) Delayed surgery: 232 (52) White, N (%) PSM analysis Early surgery: 11,765 (87.1) Delayed surgery: 11,787 (87.2) Single-center analysis Early surgery: 466 (89) Delayed surgery: 368 (82)	Stage, N (%) PSM analysis AJCC clinical T1 Early surgery: 8,608 (63.7) Delayed surgery: 8,656 (64.1) AJCC clinical T2 Early surgery: 4,903 (36.3) Delayed surgery: 4,855 (35.9) Single-center analysis AJCC clinical T1 Early surgery: 338 (65) Delayed surgery: 342 (76) TNM edition(s) NR Histology, N (%) Malignant cytologic diagnosis: 568 (1.0)	Surgical approach, N (%) PSM analysis Total: 27,022 Early surgery: 13,511 Delayed surgery: 13,511 Single-center analysis Total: 971 Early surgery: 522 Delayed surgery: 449

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Samson, 2015[240] (continued)		Charlson Comorbidity Index, N (%) PSM analysis Score=0 Early surgery: 6,459 (47.8) Delayed surgery: 6,490 (48.0) Score=1 Early surgery: 5,011 (37.1) Delayed surgery: 4,895 (36.2) Score=2+ Early surgery: 2,041 (15.1) Delayed surgery: 2,126 (15.7) Adult Comorbidity Evaluation, N (%) Single-center analysis Score=0 Early surgery: 83 (16) Delayed surgery: 37 (8) Score=1 Early surgery: 211 (40) Delayed surgery: 156 (35) Score=2	Tumor size in mm, mean (SD) PSM analysis Size Early surgery: 30.1 (22.6) Delayed surgery: 30.5 (21.3) Single-center analysis NR	

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Samson, 2015[240] (continued)		Early surgery: 125 (24) Delayed surgery: 125 (28) Score=3 Early surgery: 63 (12) Delayed surgery: 79 (18) Pulmonary hypertension Single-center analysis, N (%) Early surgery: 3 (0.6) Delayed surgery: 7 (1.6) Smoking status Single-center analysis, N (%) Current smokers Early surgery: 170 (33) Delayed surgery: 164 (37) Former smokers Early surgery: 302 (58) Delayed surgery: 244 (54) Never smokers Early surgery: 50 (10) Delayed surgery: 41 (9)		

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Samson, 2017[245] Surgery N=146,908 KQ 7 Fair	NCDB U.S. 2004-2013 c-stage I NSCLC patients who underwent operation within 1 yr of diagnosis but no preoperative chemotherapy or radiotherapy Followup, median NR Funding source Government	Age, mean Nonanatomical vs. anatomical resection (total sample) *68.75* yrs Early vs. delayed resection *68.3* yrs R0 vs. ≥R1 resection *68.5* yrs <10 vs. ≥10 lymph nodes *67.9* yrs Male, N (%) Nonanatomical vs. anatomical resection (total sample) *67,453 (45.9)* Early vs. delayed resection *66,604 (45.9)* R0 vs. ≥R1 resection *66,486 (45.9)* <10 vs. ≥10 lymph nodes *62,578 (45.8)* White, N (%) Nonanatomical vs. anatomical resection (total sample) *130,697 (89)* Early vs. delayed resection *129,131 (89)* R0 vs. ≥R1 resection *128,929 (89)* <10 vs. ≥10 lymph nodes *121,413 (88.9)*	Clinical Stage 1B, N (%) Nonanatomical vs. anatomical resection (total sample) *41,546 (28.3)* Early vs. delayed resection *40,974 (28.2)* R0 vs. ≥R1 resection *40,894 (28.2)* <10 vs. ≥10 lymph nodes *38,373 (28.1)* TNM edition(s) NR Histology, N (%) NR Tumor size, mean Nonanatomical vs. anatomical resection (total sample) *23.5 mm* Early vs. delayed resection *26.25 mm*	Surgical approach, N (%) Overall W: 29,649 (20.2) S: 6,212 (4.2) Lobectomy: 107,687 (73.3) Pneumonectomy: 3,360 (2.3) Nonanatomical vs. anatomical resection W: 29,649 (20.2) S: 6,212 (4.2) Lobectomy: 107,687 (73.3) Pneumonectomy: 3,360 (2.3) Early vs. delayed resection W: *29,367 (20.2)* S: *6,125 (4.2)* Lobectomy: *106,291 (73.3)* Pneumonectomy: *3,307 (2.3)* R0 vs. ≥R1 resection W: *28,908 (19.9)* S: *6,132 (4.2)* Lobectomy: *106,610 (73.6)* Pneumonectomy: *3,271 (2.6)* <10 vs. ≥10 lymph nodes W: *28,161 (20.6)* S: *5,750 (4.2)* Lobectomy: *99,622 (72.9)* Pneumonectomy: *3,079 (2.3)*

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Samson, 2017[245] (continued)		Charlson/Deyo comorbidity score, N (%) Nonanatomical vs. anatomical resection (total sample) Charlson/Deyo score ≥2: *20,940 (13.9)* Early vs. delayed resection (N analyzed=145,090) Charlson/Deyo score ≥2: *20,302 (14)* R0 vs. ≥R1 resection Charlson/Deyo score ≥2 (N analyzed=144,921): *20,245 (14)* <10 vs. ≥10 lymph nodes (N analyzed=136,612) Charlson/Deyo score ≥2: *19,167 (14)*	R0 vs. ≥R1 resection *28.35 mm* <10 vs. ≥10 lymph nodes *26.4 mm* Tumor size, N (%) <2 cm: 3,675 (59.2)	

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Sawabata, 2011[190] Surgery N=9,083 eligible (of 11,663 total) KQ 6 Fair	Japanese Joint Committee of Lung Cancer Registry (JJCLCR) Japan 2004-2010 Pathological diagnosis of any type of lung cancer at a participating institution, diagnosis obtained in 2004, and treated by surgery Followup, median 2 to 78 mos Funding source NR	Age, median (range) NR Male, N (%) NR Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) c-stage 1A: 6,295 (54) c-stage 1B: 2,788 (23.9) p-stage 1A: 5,611 (48.1) p-stage 1B: 2,398 (20.4) TNM edition(s) 6th & 7th editions Histology, N (%) NR Tumor size, mean (SD) NR	Surgical approach, N (%) NR
Scheel, 2015[170] Surgery N=800 KQs 6, 7 Fair	NR U.S. 2000-2012 Patients who underwent initial resection by lobectomy or SLR of p-stage I NSCLC between January 2000 and December 2012 at Washington University School of Medicine Followup, median (range) NR Funding source Government	Age, mean (SD) NR for overall sample, but range from 64.3-65.5 across surg exp groups Male, N (%) *361 (45.1)* White, N (%) *690 (86.3)* Smoking status, N (%) Never: *96 (12.0)* Past: *421 (52.6)* Current: *283 (35.4)*	Stage, N (%) p-stage I: 800 (100) TNM edition(s) NR Histology, N (%) NR Tumor size, N (%) NR	Surgical approach, N (%) All Resections: 800 L: 638 (79.8) SLR: 162 (20.2)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers **Author, Year** **Treatment Type(s)** **N Enrolled** **KQs Addressed** **Quality**	**Study Characteristics** **Study or Database Name** **Country** **Study Years** **Eligibility Criteria** **Followup** **Funding Source**	**Baseline Patient Characteristics** **Age** **Gender** **Race/Ethnicity** **Comorbidities**	**NSCLC Characteristics** **Stage** **TNM Edition(s)** **Histology** **Tumor Size**	**Treatment Characteristics** **Surgical Approach** **SBRT/SABR Dosing and Frequency**
Schuchert, 2012[248] Surgery N=899 KQ 7 Fair	NA U.S. 1999-2010 Patients with p-stage 1 NSCLC without multicentric disease and undergoing complete anatomic segmentectomy or lobectomy, but not preoperative radiotherapy or chemotherapy Followup, median 37 mos Funding source NR	Age, mean (SD) (range) Total: 69.2 yrs (NR) (22-91 yrs) Anatomic S: 70.0 yrs (8.6 yrs) (40 to 91 yrs) L: 68.4 yrs (10.1 yrs) (22 to 90 yrs) Male, N (%) Total: 427 *(47.5)* Anatomic S: 145 *(47.5)* L: 282 *(47.5)* Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) <u>p-stage 1A</u> Total: 477 *(53.1)* Anatomic S: 187 *(61.3)* L: 290 *(57.5)* <u>p-stage 1B</u> Total: 422 *(46.9)* Anatomic S: 118 *(38.7)* L: 304 *(60.3)* TNM edition(s) 6th edition Histology, N (%) <u>Adenocarcinoma</u> Overall: *487 (54.2)* Anatomic S: 161 (52.8) L: 326 (54.9) <u>Squamous cell</u> Overall: *295 (32.8)* Anatomic S: 96 (31.5) L: 199 (33.5) <u>Other NSCLC</u> Overall: *117 (13.0)* Anatomic S: 48 (15.7) L: 69 (11.6) Tumor size, median (IQR) (range) Overall: NR Anatomic S: 2.0 cm (1.5 to 2.8 cm) (0.2 to 5.0 cm) L: 2.5 cm (1.8 to 4.0 cm) (0.2 to 12 cm)	Surgical approach, N (%) Anatomic S: 305 (33.9) L: 594 (66.1) <u>Open procedure</u> Total: *489 (54.4)* Anatomic S: 120 (39.3) L: 369 (62.1) <u>VATS approach</u> Total: *410 (45.6)* Anatomic S: 185 (60.7) L: 225 (37.9)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers **Author, Year** **Treatment Type(s)** **N Enrolled** **KQs Addressed** **Quality**	**Study Characteristics** **Study or Database Name** **Country** **Study Years** **Eligibility Criteria** **Followup** **Funding Source**	**Baseline Patient Characteristics** **Age** **Gender** **Race/Ethnicity** **Comorbidities**	**NSCLC Characteristics** **Stage** **TNM Edition(s)** **Histology** **Tumor Size**	**Treatment Characteristics** **Surgical Approach** **SBRT/SABR Dosing and Frequency**
Shapiro, 2012[247] Surgery N=4,975 KQ 7 Fair	SEER U.S. 1992-2002 Patients with Stage I NSCLC aged ≥65 years who underwent lobectomy, but no pre-operative chemotherapy or radiotherapy Followup, median NR Funding source Government	Age, N (%) 65-69 yrs: *1,421 (28.6)* 70-74 yrs: *1,662 (33.4)* 75-79 yrs: *1,244 (25)* ≥80 yrs: *648 (13)* Male, N (%) *2,565 (51.6)* White, N (%) *4,348 (87.4)* Comorbidities, N (%) Charlson/Deyo score 0-1, N (%): *4,238 (85.2)* Charlson/Deyo score 2-3, N (%): *479 (9.6)* Charlson/Deyo score ≥4, N (%): *258 (5.2)*	Stage, N (%) NR TNM edition(s) 5th edition Histology, N (%) Adenocarcinoma: *2,205 (44.3)* Bronchioalveolar carcinoma: *219 (4.4)* Squamous carcinoma: *1,631 (32.8)* Large cell carcinoma: *267 (5.4)* Other: *653 (13.1)* Tumor size, N (%) ≤20 mm: *1,473 (29.6)* 21-30 mm: *1,526 (30.7)* 31-50 mm: *1,409 (28.3)* 51-70 mm: *403 (8.1)* ≥71 mm: *164 (3.3)*	Surgical approach, N (%) L: 4,975 (100)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Shirvani, 2012[237] Surgery & SBRT/SABR N=10,923 KQ 7 Fair	SEER-Medicare database U.S. 2001-2007 Patients aged >66 years diagnosed with early-stage (IA-IB) NSCLC without prior or future malignancy within 120 days of index cancer and who were treated with SABR, but not nonstandard therapies (e.g., chemotherapy), reported in the SEER-Medicare cohort demographic Followup, median 3.2 yrs Cancer Prevention & Research Institute of Texas; NCI; and Varian Medical Systems	Age, median 75 yrs Age 66-69, N (%) SLR: 234 (18) SABR: 11 (9) L: 1,408 (22) Age 70-74, N (%) SLR: 362 (28) SABR: 20 (16) L: 2,055 (31) Age 75-79, N (%) SLR: 392 (31) SABR: 29 (23) L: 1,907 (29) Age ≥80, N (%) SLR: 289 (23) SABR: 64 (52) L: 1,161 (18) Male, N (%) SLR: 571 (45) SABR: 49 (40) L: 3,011 (46) White, N (%) SLR: 1,184 (93) SABR: >11 (>90) L: 5,927 (91)	Stage, N (%) NR TNM edition(s) NR Histology, N (%) NSCLC, NOS SLR: 84 (7) SABR: 34 (27) L: 373 (6) Adenocarcinoma SLR: 749 (59) SABR: 53 (43) L: 3,931 (60) Squamous cell carcinoma SLR: 389 (30) SABR: 36 (29) L: 1,982 (30)	Surgical approach, N (%) SLR: 1,277 (11.7) L: 6,531 (58.9) SABR patients, N (%) 124 (1.1) SABR dosing NR

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Shirvani, 2012[237] (continued)		Charlson Comorbidity Index, N (%) Score=0 SLR: 339 (27) SABR: 28 (23) L: 2,814 (43) Score=1 SLR: 447 (35) SABR: 42 (34) L: 2,042 (31) Score ≥2 SLR: 457 (36) SABR: 54 (44) L: 1,495 (23) Missing Total: 366 (3)	Tumor size, N (%) ≤2.0 cm SLR: 820 (64) SABR: 48 (39) L: 2,723 (42) 2.1-3.0 cm SLR: 316 (25) SABR: 48 (39) L: 2,188 (34) 3.1-5.0 cm SLR: 141 (11) SABR: 28 (23) L: 1,620 (25)	

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Shirvani, 2014[241] Surgery & SBRT/SABR N=9,093 KQ 7 Fair	SEER-Medicare U.S. 2003-2009 Patients with early-stage, node-negative, pathologically confirmed NSCLC who underwent lobectomy, SLR, or SABR without undergoing any nonstandard therapies Followup, median (range) NR Funding source Government	Age, N (%) <u>66 to 69 yrs</u> L: 1515 (21.0) SLR: 235 (15.7) SABR: 39 (10.2) <u>70 to 74 yrs</u> L: 2182 (30.2) SLR: 415 (27.7) SABR: 71 (18.6) <u>75 to 79 yrs</u> L: 2069 (28.7) SLR: 435 (29.1) SABR: 94 (24.6) <u>≥80 yrs</u> L: 1449 (20.1) SLR: 411 (27.5) SABR: 178 (46.6) Male, N (%) L: 3365 (46.6) SLR: 693 (46.3) SABR: 143 (37.4) White, N (%) L: 6456 (89.5) SLR: 1360 (90.9) SABR: 340 (89.0) Charlson Comorbidity Index, N (%) <u>0</u> L: 4368 (60.5) SLR: 792 (52.9) SABR: 170 (44.5)	Stage, N (%) NR TNM edition(s) NR Histology, N (%) <u>NSCLC, NOS</u> L: 366 (5.1) SLR: 90 (6.0) SABR: 82 (21.5) <u>Adenocarcinoma</u> L: 4371 (60.6) SLR: 866 (57.9) SABR: 178 (46.6) <u>Squamous cell carcinomas</u> L: 2236 (31.0) SLR: 482 (32.2) SABR: >110 (>25) <u>Large cell cancer</u> L: 242 (3.4) SLR: 58 (3.9) SABR: <11 (<5)	Surgical approach, N (%) L: 7,215 (*79.3*) SLR: 1,496 (*16.5*) SABR patients, N (%) 382 (*4.2*) SABR dosing NR

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Shirvani, 2014[241] (continued)		1 L: 1700 (23.6) SLR: 379 (25.3) SABR: 108 (28.3) ≥ 2 L: 1147 (15.9) SLR: 325 (21.7) SABR: 104 (27.2) COPD L: 4459 (61.8) SLR: 1136 (75.9) SABR: 296 (77.5)	Tumor size by T stage, N (%) T1a (0.0 to 2.0 cm) L: 3169 (43.9) SLR: 964 (64.4) SABR: 153 (40.1) T1b (2.1 to 3.0 cm) L: 2370 (32.8) SLR: 355 (23.7) SABR: 153 (40.1) T2a (3.1 to 5.0 cm) L: 1676 (23.2) SLR: 177 (11.8) SABR: 76 (19.9)	

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Speicher, 2016[187] Surgery N=39,403 KQ 6 Fair	NCDB U.S. 2003-2006 Patients with c-stage 1A T1N0M0 NSCLC undergoing a lobectomy or SLR without induction therapy Followup, median 6.3 yrs Funding source Government, other unspecified	Age, mean (SD); Median Total: 67.4 yrs (9.8 yrs); 68.0 yrs L: 66.7 yrs (9.7 yrs); 67.0 yrs SLR: 69.6 yrs (9.5 yrs); 70.0 yrs Male, N (%) Total: 17,112 (43.4) L: 12,970 (43.6) SLR: 4,142 (42.8) White, N (%) Total: 35,266 (89.5) L: 26,491 (89.1) SLR: 8,775 (90.8) Charlson Comorbidity Index, N (%) (for initial sample only, but unclear if the same for survival analysis sample) <u>Score=0</u> Total: 18,438 (46.8) L: 14,615 (49.1) SLR: 3,823 (39.5) <u>Score=1</u> Total: 15,110 (38.3) L: 11,053 (37.2) SLR: 4,057 (42.0) <u>Score ≥2</u> Total: 5,855 (14.9) L: 4,068 (13.7) SLR: 1,787 (18.5)	Stage, N (%) c-stage T1N0M0: 39,403 (100) TNM edition(s) 5th, 6th, and 7th editions Histology, N (%) NR Tumor size, mean (SD) (for initial sample only, but unclear if the same for survival analysis sample) Total: 2.0 cm (0.9 cm) L: 2.0 cm (0.9 cm) SLR: 1.7 cm (0.7 cm)	Surgical approach, N (%) (for initial sample only, but unclear if the same for survival analysis sample) L: 29,736 (75.5) SLR: 9,667 (24.5) <u>SLR subtypes</u> W: 8,192 *(84.7)* S: 1,475 *(15.3)*

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Stephens, 2014[182] Surgery N=963 KQs 6, 7 Fair	NA U.S. 2002-2011 Consecutive patients with c-stage 1 NSCLC undergoing VATS or open lobectomy, but not other types of lobectomy, preoperative chemotherapy, or radiotherapy Followup, median NR Funding source NR	Age, mean (SD) Total: NR VATS L: 66 yrs (10 yrs) Open L: 67 yrs (10 yrs) Male, N (%) Total: *454 (47.1)* VATS L: 134 (44) Open L: 320 (49) Race/ethnicity NR Comorbidities, N (%) COPD Total: *135 (14.0)* VATS L: 42 (14) Open L: 93 (14)	Stage, N (%) Clinical T1 Total: *613 (63.7)* VATS L: 229 (75) Open L: 384 (58) Clinical T2 Total: *350 (36.3)* VATS L: 78 (25) Open L: 272 (42) TNM edition(s) Clinical: 6th edition Pathologic: 7th edition Histology, N (%) Adenocarcinoma Total: *658 (68.3)* VATS L: 231 (75) Open L: 427 (65) Squamous cell Total: *226 (23.5)* VATS L: 54 (18) Open L: 172 (26) Other NSCLC Total: *79 (8.2)* VATS L: 22 (7) Open L: 57 (9) Tumor diameter, mean (SD) Total: *2.9* cm (NR) VATS L: 2.5 cm (1 cm) Open L: 3.2 cm (2 cm)	Surgical approach, N (%) Planned VATS L: 307 *(31.9)* Open L: 656 *(68.1)* Actual (taking conversion into account) VATS lobectomy: *285 (29.6)* Open lobectomy: *678 (70.4)*

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers **Author, Year** **Treatment Type(s)** **N Enrolled** **KQs Addressed** **Quality**	**Study Characteristics** **Study or Database Name** **Country** **Study Years** **Eligibility Criteria** **Followup** **Funding Source**	**Baseline Patient Characteristics** **Age** **Gender** **Race/Ethnicity** **Comorbidities**	**NSCLC Characteristics** **Stage** **TNM Edition(s)** **Histology** **Tumor Size**	**Treatment Characteristics** **Surgical Approach** **SBRT/SABR Dosing and Frequency**
Stokes, 2018[251] Surgery & SBRT/SABR N=84,839 KQ 7 Fair	NCDB U.S. 2004-2013 Patients with T1-2N0M0 NSCLC as first primary malignancy and treated with surgery or SBRT at a CoC-accredited facility, without missing treatment or followup timing data Followup, median NR Funding source University, other unspecified source	Age, N (%) <u>≤55 years</u> All surgery: 9,816 (12.8) SBRT: 241 (2.9) <u>56-60 years</u> All surgery: 8,472 (11.1) SBRT: 416 (5.1) <u>61-65 years</u> All surgery: 12,069 (15.8) SBRT: 800 (9.7) <u>66-70 years</u> All surgery: 15,338 (20.0) SBRT: 1,279 (15.6) <u>71-75 years</u> All surgery: 14,030 (18.3) SBRT: 1,556 (18.9) <u>76-80 years</u> All surgery: 10,761 (14.0) SBRT: 1,720 (20.9) <u>≥81 years</u> All surgery: 6,137 (8.0) SBRT: 2,204 (26.8) Male, N (%) All surgery: 34,427 (44.9) SBRT: 3,601 (43.8) White, N (%) All surgery: 67,744 (88.4) SBRT: 7,314 (89.0)	Stage, N (%) <u>T1a</u> All surgery: 32,802 (42.8) SBRT: 3,293 (40.1) <u>T1b</u> All surgery: 19,468 (25.4) SBRT: 2,688 (32.7) <u>T1 NOS</u> All surgery: 2,472 (3.2) SBRT: 154 (1.9) <u>T2a</u> All surgery: 21,881 (28.6) SBRT: 2,081 (25.3) TNM edition(s) 7th edition Histology, N (%) <u>Adenocarcinoma</u> All surgery: 41,110 (53.7) SBRT: 3,511 (42.7) <u>Squamous cell</u> All surgery: 20,031 (26.1) SBRT: 2,831 (34.5) <u>Other</u> All surgery: 15,482 (20.2) SBRT: 1,874 (22.8)	Surgical approach, N (%) All surgery: 76,623 *(90.3)* P: *1,532* (2.0) L: *59,536* (77.7) SLR: *15,555* (20.3) SBRT patients, N (%) 8,216 *(9.7)* SBRT dosing, N (%) 50 Gy x 5 fx: *1,586* (19.3) 60 Gy x 3 fx: *1,454* (17.7) 48 Gy x 4 fx: *1,397* (17.0) 54 Gy x 3 fx: *1,150* (14.0) Other dosage & fx schedules: *2,629 (32.0)*

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Stokes, 2018[251] (continued)		Charlson Comorbidity Index, N (%) Score=0 All surgery: 37,066 (48.4) SBRT: 4,602 (56.0) Score=1 All surgery: 28,150 (36.7) SBRT: 2,210 (26.9) Score ≥2 All surgery: 11,407 (14.9) SBRT: 1,404 (17.1)	Tumor size, mean (SD) NR	
Strand, 2006[194] Surgery N=1,375 eligible (of 3,211 total) KQ 6 Good	Cancer Registry of Norway Norway 1993-2002 All patients diagnosed with lung cancer in Norway (mandatorily reported to registry) who had a surgical procedure Followup, median 5 yrs Funding source NR	Age, median (range) NR Male, N (%) NR Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) p-stage of N enrolled (n=2,144), N (%) I: 1375 *(64.1)* II: 532 *(24.8)* III: 196 *(9.1)* IV: 41 *(1.9)* p-stage I breakdown, N (% of 1375): IA: 559 *(40.7)* IB: 816 *(59.3)* TNM edition(s) 5th edition Histology, N (%) NR Tumor size, mean (SD) NR	Surgical approach, N (%) L: NR Bi-L: NR P: NR SLR: NR

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Su, 2014[174] Surgery N=1,023 KQ 6 Fair	Alliance trial ACOSOG Z0030 U.S. NR Patients with a tissue diagnosis of c-stage T1-2 NSCLC, N0 or nonhilar N1, M0 before randomization and ECOG performance status <3 who received surgical resection by means of P, L, Bi-L, or S Followup, median (range) 6.7 yrs Funding source NR	Age, median (range) NR Male, N (%) NR Race/ethnicity NR Comorbidities NR	c-stage, N (%) T1: 578 (57) T2: 440 (43) TNM edition(s) NR Histology, N (%) NR Tumor size, N (%) NR	Surgical approach, N (%) P: NR L: NR Bi-L: NR S: NR

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Sun, 2017[197] SBRT/SABR N=73 KQs 6, 7 Fair	NA U.S. 2005-2013 Patients with a histologically confirmed, c-stage IA (T1N0M0) or Stage IB (T2aN0M0) NSCLC who underwent SABR due to medical inoperability or if they had operable disease but elected to undergo SABR. Patients with a prior history of lung cancer who were free of lung cancer for >5 years for the same histology or >2 years for a different histology. Followup, median (IQR) 7.2 yrs (4.6 to 8.3 yrs) National Cancer Institute	Age, median (range) 71.8 yrs (54.7 to 91.8 yrs) Male, N (%) 32 (49.2) Race/ethnicity NR Smoking status, N (%) Past or current: 57 (87.7) Never: 8 (12.3)	Stage, N (%) T1a: 38 (58.5) T1b: 24 (36.9) T2 (T2a: ≤ 5 cm, pleural invasion): 3 (4.6) TNM edition(s) 7th edition Histology, N (%) Adenocarcinoma: 30 (46.2) Squamous: 26 (40.0) NSCC NOS: 9 (13.8) Maximum tumor diameter, median (range) 1.9 cm (0.7 to 4.0 cm)	SABR patients, N (%) 73 (100) SABR dosing, N (%) 50 Gy x 4 fx: 63 (*96.9*) 45 Gy x 4 fx: 1 (*1.5*) 50 Gy X 3 fx: 1 (*1.5*)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Taremi, 2012[261] SBRT/SABR N=46 KQ 7 Fair	NA Canada 2004-2008 Medically inoperable patients with T1-2N0M0 NSCLC treated with 18-20 Gy x 3 fx and with >6 mos followup Followup, median 24.9 mos Funding source Industry, other unspecified	Age, median (range) 72.8 yrs (48.3 to 89.6 yrs) Male, N (%) 22 (*48*) Race/ethnicity NR COPD, N (%) 29 (*63*)	Stage, N (%) All patients had T1-2N0M0 NSCLC TNM edition(s) NR Histology, N (%) NR Tumor size, mean (SD) 2.6 cm (1.2 cm)	SBRT patients, N (%) 46 (100) SBRT dosing, N (%) 18 or 20 Gy x 3 fx: 46 (100)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Taremi, 2012[264] SBRT/SABR N=108 KQ 7 Fair	NA Canada 2004-2008 Medically inoperable patients with synchronous Stage T1-T2N0M0 NSCLC, either biopsy-proven or identified by "suspicious" pulmonary lesions according to evidence of interval progression on ≥2 serial CT imaging studies (minimum of 1 mo apart) and/or increased FDG uptake on PET scan, and ECOG performance status of 0-3 Followup, median 19.1 mos Funding source Government, private	Age, mean (SD) 72.6 yrs (48.3 to 90 yrs) Male, N (%) 53 *(49.1)* Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) T stage 1 (≤3 cm): 86 *(79.6)* T stage 2 (>3 cm): 28 *(20.4)* TNM edition(s) NR Histology, N (%) Adenocarcinoma: 34 *(29.8)* Squamous cell carcinoma: 22 *(19.3)* Large cell carcinoma: 6 *(5.3)* NSCLC, NOS: 19 *(16.7)* No biopsy or nondiagnostic sample: 33 *(28.9)* Tumor size, mean (SD) 2.4 cm (1.1 cm)	SBRT patients, N (%) 108 (100) SBRT dosing, N (%) 60 Gy x 3 fx: 31 *(27.2)* 54 Gy x 3 fx: 20 *(17.5)* 48 Gy x 4 fx: 43 *(37.7)* 60 Gy x 8 fx: 9 *(7.9)* 50 Gy x 10 fx: 11 *(9.6)*

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Study Identifiers **Author, Year** **Treatment Type(s)** **N Enrolled** **KQs Addressed** **Quality**	**Study Characteristics** **Study or Database Name** **Country** **Study Years** **Eligibility Criteria** **Followup** **Funding Source**	**Baseline Patient Characteristics** **Age** **Gender** **Race/Ethnicity** **Comorbidities**	**NSCLC Characteristics** **Stage** **TNM Edition(s)** **Histology** **Tumor Size**	**Treatment Characteristics** **Surgical Approach** **SBRT/SABR Dosing and Frequency**
Tsutani, 2014[179] Surgery N=618 KQs 6, 7 Good	NA Japan 2005-2010 Patients with clinical T1N0 M0 Stage IA NSCLC adenocarcinoma (no synchronous multiple tumors) who underwent preoperative staging using HRT and FDG-PET/CT and had definitive histopathologic diagnosis, followed by complete curative resection without neoadjuvant chemotherapy or radiotherapy Followup, median 42.9 mos Funding source NR	Age, mean (range) *66 yrs* (31 to 89 yrs) Male, N (%) *272 (44)* Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) Clinical T1a: *354 (57.3)* Clinical T1b: *264 (42.7)* TNM edition(s) 7th edition Histology, N (%) Adenocarcinoma: 618 (100) Adenocarcinoma in situ: *97 (15.7)* Tumor size, mean Whole tumor: 2.0 cm Solid tumor: 1.1 cm	Surgical approach, N (%) L: *383 (62.0)* SLR: *235 (38.0)* S: *98 (15.9)* W: *137 (22.2)*

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Ubels, 2015[206] SBRT/SABR N=39 KQs 6, 7 Fair	NA The Netherlands 2006-2008 Patients who refused surgery or had inoperable Stage T1-2N0M0 NSCLC with pathological confirmation of diagnosis and no progressive disease 3 weeks after treatment Followup, median 38 mos Funding source NR	Age, median (range) 77 yrs (55 to 87 yrs) Male, N (%) NR Race/ethnicity NR Comorbidities Charlson Comorbidity Index, N (%) Score=0-2: 20 (51) Score=3: 13 (33) Score ≥3: 6 (15) COPD, N (%) 22 (56)	Stage, N (%) Stage T1: 17 (44) Stage T2: 21 (54) Stage T3: 1 (3) TNM edition(s) NR Histology, N (%) Adenocarcinoma: 8 (21) Squamous cell: 14 (36) Large cell carcinoma: 13 (33) Other: 4 (10) Tumor size, mean (SD) NR	SBRT patients, N (%) 39 (100) SBRT dosing, N (%) 60 Gy x 3 fx: 30 *(76.9)* 48-50 Gy x 5-6 fx: 7 *(17.9)* 45 Gy x 3 fx: 2 *(5.1)*

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Study Identifiers **Author, Year** **Treatment Type(s)** **N Enrolled** **KQs Addressed** **Quality**	**Study Characteristics** **Study or Database Name** **Country** **Study Years** **Eligibility Criteria** **Followup** **Funding Source**	**Baseline Patient Characteristics** **Age** **Gender** **Race/Ethnicity** **Comorbidities**	**NSCLC Characteristics** **Stage** **TNM Edition(s)** **Histology** **Tumor Size**	**Treatment Characteristics** **Surgical Approach** **SBRT/SABR Dosing and Frequency**
Valle, 2016[246] Surgery & SBRT/SABR N=*1,367* KQ 7 Fair	NCCN U.S. 2007-2011 Patients receiving primary thoracic surgery or SBRT at NCCN institution for Stage 1 NSCLC within 120 days of diagnosis, no previous diagnosis within the previous 2 years or another invasive malignancy within the past 5 years, and sufficient followup Followup, median NR Funding source NR	Age, median (range) NR Male, N (%) NR Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) NR TNM edition(s) 6th edition Histology, N (%) NR Tumor size, mean (SD) NR	Surgical approach, N (%) 1,183 *(86.5)* SBRT patients, N (%) 184 *(13.5)* SBRT dosing, N (%) NR

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Videtic, 2014[271] SBRT/SABR N=80 KQ 7 Fair	NA U.S. 2009-2012 Medically inoperable patients who received treated with single-fx SBRT, including those potentially eligible for the RTOG 0915 or RPCI trials based on tumor size and peripheral location requirements, but who missed eligibility criteria for enrollment (e.g., biopsy result showing proof of malignancy) and received single-fx SBRT up off-protocol Followup, median (range) Single-fx SBRT at 30 Gy: 18.7 mos (1.8 to 43.0 mos) Single-fx SBRT at 34 Gy: 17.8 mos (0.1 to 39.4 mos) Funding source NR	Age, median (range) Single-fx SBRT at 30 Gy: 75 (48 to 91) Single-fx SBRT at 34 Gy: 73 (53 to 84) Male, N (%) Single-fx SBRT at 30 Gy: 36 (65.5) Single-fx SBRT at 34 Gy: 11 (44) Race/ethnicity NR Comorbidities, N (%) Current smoking status Single-fx SBRT at 30 Gy: 10 *(18.2)* Single-fx SBRT at 34 Gy: 8 (32) Pack-year history, median (range) Single-fx SBRT at 30 Gy: 50 (0 to 100) Single-fx SBRT at 34 Gy: 55 (5 to 125)	Stage, N (%) Clinical T1a Single-fx SBRT at 30 Gy: 49 (89.1) Single-fx SBRT at 34 Gy: 24 (96) Clinical T1b Single-fx SBRT at 30 Gy: 6 (10.9) Single-fx SBRT at 34 Gy: 1 (4) TNM edition(s) NR Histology, N (%) Adenocarcinoma Single-fx SBRT at 30 Gy: 12 (32) Single-fx SBRT at 34 Gy: 8 (43) Squamous cell carcinoma Single-fx SBRT at 30 Gy: 14 (37) Single-fx SBRT at 34 Gy: 9 (47) Other Single-fx SBRT at 30 Gy: 4 (10) Single-fx SBRT at 34 Gy: 0 (0) Nondiagnostic Single-fx SBRT at 30 Gy: 8 (21) Single-fx SBRT at 34 Gy: 2 (10) Tumor size, median (range) Single-fx SBRT at 30 Gy: 1.7 cm (0.9 to 4.8 cm) Single-fx SBRT at 34 Gy: 1.7 cm (1.0 to 4.0 cm)	SBRT patients, N (%) 80 (100) SBRT dosing, N (%) 30 Gy x 1 fx: 55 (69) 34 Gy x 1 fx: 25 (31)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Videtic, 2015[263] SBRT/SABR N=84 KQ 7 Fair	RTOG 0915 U.S. 2009-2011 Patients with cytologic or histologic diagnosis of NSCLC >2 cm staged as T1-T2N0M0 and based on CT and PET imaging; Zubrod performance status of 0-2; deemed medically inoperable by thoracic oncology specialist or declining surgery despite being operable; and no prior or planned use of concomitant antineoplastic therapy during SBRT protocol Followup, median 30.2 mos Funding source Government	Age, median (range) SBRT at any dose: 75 yrs (52 to 89 yrs) SBRT 34 Gy x 1 fx: 75 yrs (57 to 89 yrs) SBRT 48 Gy x 4 fx: 75 yrs (52 to 87 yrs) Male, N (%) <u>Male</u> SBRT at any dose: *38 (45.2)* SBRT 34 Gy x 1 fx: 16 (41.0) SBRT 48 Gy x 4 fx: 22 (48.9) Race/ethnicity NR Comorbidities, N (%) NR	Stage, N (%) <u>T1</u> SBRT at any dose: *72 (85.7)* SBRT 34 Gy x 1 fx: 32 (82) SBRT 48 Gy x 4 fx: 40 (88.9) <u>T2</u> SBRT at any dose: *12 (14.3)* SBRT 34 Gy x 1 fx: 7 (18.0) SBRT 48 Gy x 4 fx: 5 (11.1) TNM edition(s) 6th edition Histology, N (%) <u>Adenocarcinoma</u> SBRT at any dose: *49 (58.3)* SBRT 34 Gy x 1 fx: 23 (59.0) SBRT 48 Gy x 4 fx: 26 (57.8) <u>Squamous cell</u> SBRT at any dose: *25 (29.8)* SBRT 34 Gy x 1 fx: 9 (23.1) SBRT 48 Gy x 4 fx: 16 (35.6) <u>NSCLC NOS</u> SBRT at any dose: *10 (11.9)* SBRT 34 Gy x 1 fx: 7 (17.9) SBRT 48 Gy x 4 fx: 3 (6.7) Max tumor diameter, median (range) SBRT at any dose: 2.0 cm (0.8 to 4.98 cm) SBRT 34 Gy x 1 fx: 2.0 cm (1.0 to 4.98 cm) SBRT 48 Gy x 4 fx: 2.0 cm (0.8 to 4.3 cm)	SBRT patients, N (%) 84 (100) SBRT dosing, N (%) 34 Gy x 1 fx: 39 *(46.4)* 48 Gy x 4 fx: 45 *(53.6)*

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Yang, 2016[250] Surgery N=20,191 KQ 7 Fair	NCDB U.S. 2010-2012 Patients diagnosed with clinical T Stage 1-2, N0, M0 NSCLC, undergoing lobectomy, with available data on surgical approach, and no history of unrelated malignancy Followup, median NR Funding source Government, professional association	Age, median (IQR) Open surgery vs. MIS – PMS subset (N=18,780) Open L: 68 yrs (60 to 74 yrs) MIS L: 68 yrs (60 to 74 yrs) VATS vs. robotic L – PMS subset (N=3,876) VATS L: 69 yrs (62 to 74 yrs) Robotic L: 68 yrs (61 to 74 yrs) Male, N (%) Open surgery vs. MIS – PMS subset (N=18,780) Open L: 5,385 (57.3) MIS L: 5,375 (57.2) VATS vs. robotic L – PMS subset (N=3,876) VATS L: 1,079 (55.7) Robotic L: 1,099 (56.7) White, N (%) Open surgery vs. MIS – PMS subset (N=18,780) Open L: 8,336 (88.8) MIS L: 8,263 (88) VATS vs. robotic L – PMS subset (N=3,876) VATS L: 1,721 (88.8) Robotic L: 1,687 (87)	Stage, N (%) Open surgery vs. MIS – PMS subset (N=18,780) Clinical T status T1 Open L: 6,685 (71.2) MIS L: 6,598 (70.3) T2 Open L: 2,705 (28.8) MIS L: 2,792 (29.7) Pathologic T status T0 (in situ) Open L: 7 (0.1) MIS L: 12 (0.1) T1 Open L: 5,398 (59.7) MIS L: 5,259 (57.8) T2 Open L: 3,222 (35.6) MIS L: 3,386 (37.2) T3 Open L: 362 (4.0) MIS L: 393 (4.3) T4 Open L: 56 (0.6) MIS L: 44 (0.5) Pathologic N status N0 Open L: 7,861 (87.8) MIS L: 7,969 (88.5)	Surgical approach, N (%) Open surgery vs. MIS – PMS subset (N=18,780) MIS L: 9,390 (50) VATS L: 9,390 (50) VATS vs. robotic L – PMS subset (N=3,876) Robotic L: 1,938 (50) Open L: 1,938 (50)

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Yang, 2016[250] (continued)		Comorbidities, N (%) Open surgery vs. MIS – PSM subset (N=18,780) Charlson=0 Open L: 4,747 (50.6) MIS L: 4,670 (49.7) Charlson=1 Open L: 3,426 (36.5) MIS L: 3,446 (36.7) Charlson=2+ Open L: 1,217 (13.0) MIS L: 1,274 (13.6) VATS vs. robotic L – PSM subset (N=3,876) Charlson=0 VATS L: 863 (44.5) Robotic L: 889 (45.9) Charlson=1 VATS L: 811 (41.8) Robotic L: 762 (39.3) Charlson=2+ VATS L: 264 (13.6) Robotic L: 287 (14.8)	N1 Open L: 728 (8.1) MIS L: 691 (7.7) N2 Open L: 366 (4.1) MIS L: 338 (3.8) N3 Open L: 1 (0.0) MIS L: 3 (0.0) Pathologic M status M0 Open L: 9,300 (99.8) MIS L: 9,295 (99.7) M1 Open L: 21 (0.2) MIS L: 26 (0.3) VATS vs. robotic L – PMS subset (N=3,876) Clinical T status T1 VATS L: 1,445 (74.6) Robotic L: 1,401 (72.3) T2 VATS L: 493 (25.4) Robotic L: 537 (27.7) Pathologic T status T0 (in situ) VATS L: 5 (0.3) Robotic L: 3 (0.2) T1 VATS L: 1,143 (61.0) Robotic L: 1,112 (59.5)	

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Yang, 2016[250] (continued)			T2 VATS L: 625 (33.4) Robotic L: 665 (35.6) T3 VATS L: 87 (4.6) Robotic L: 82 (4.4) T4 VATS L: 13 (0.7) Robotic L: 7 (0.4) Pathologic N status N0 VATS L: 1,661 (89.4) Robotic L: 1,652 (89.0) N1 VATS L: 138 (7.4) Robotic L: 136 (7.3) N2 VATS L: 65 (3.5) Robotic L: 67 (3.6) N3 VATS L: 0 (0) Robotic L: 2 (0.1) Pathologic M status M0 VATS L: 1,910 (99.7) Robotic L: 1,910 (99.7) M1 VATS L: 6 (0.3) Robotic L: 6 (0.3) TNM edition(s) 7th edition	

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Yang, 2016[250] (continued)			Histology, N (%) Open surgery vs. MIS – PMS subset (N=18,780) Well differentiated Open L: 1,813 (20.5) MIS L: 1,826 (20.5) Moderately differentiated Open L: 4,167 (47.2) MIS L: 4,255 (47.9) Poorly differentiated Open L: 2,758 (31.2) MIS L: 2,722 (30.6) Undifferentiated/anaplastic Open L: 97 (1.1) MIS L: 86 (1) VATS vs. robotic L – PMS subset (N=3,876) Well differentiated VATS L: 359 (19.6) Robotic L: 415 (22.5) Moderately differentiated VATS L: 897 (48.9) Robotic L: 865 (46.9) Poorly differentiated VATS L: 565 (30.8) Robotic L: 551 (29.9) Undifferentiated/anaplastic VATS L: 13 (0.7) Robotic L: 14 (0.8)	

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Eligibility Criteria Followup Funding Source	Baseline Patient Characteristics Age Gender Race/Ethnicity Comorbidities	NSCLC Characteristics Stage TNM Edition(s) Histology Tumor Size	Treatment Characteristics Surgical Approach SBRT/SABR Dosing and Frequency
Yang, 2016[250] (continued)			Tumor size, mean (SD) Open surgery vs. MIS (N=18,780) Pathologic tumor size Open L: 2.7 cm (2.1 cm) MIS L: 2.7 cm (2.1 cm) VATS vs. Robotic L (N=3,876) Pathologic tumor size VATS L: 2.6 cm (1.4 cm) Robotic L: 2.7 cm (2.3 cm)	
Zhai, 2014[172] Surgery N=724 (subset of sample with Stage 1 NSCLC) KQ 6 Fair	NA U.S. 1992-2010 Patients >18 years old with pathologically confirmed newly diagnosed NSCLC (Stages 1-2) and not receiving adjuvant therapy who were consecutively recruited and followed Followup, median 41 mos Funding source Government	Age, mean (SD) NR Male, N (%) NR Race/ethnicity NR Comorbidities *271* (*37.4*)	Stage, N (%) c-stage 1A: 538 (59.6) c-stage 1B: 186 (20.6) TNM edition(s) NR Histology, N (%) NR Tumor size, N (%) NR	Surgical approach, N (%) W: NR L: NR Others: NR

Appendix E Table 4. KQs 6 and 7: Study and Patient Characteristics Table

Study Identifiers **Author, Year** **Treatment Type(s)** **N Enrolled** **KQs Addressed** **Quality**	**Study Characteristics** **Study or Database Name** **Country** **Study Years** **Eligibility Criteria** **Followup** **Funding Source**	**Baseline Patient Characteristics** **Age** **Gender** **Race/Ethnicity** **Comorbidities**	**NSCLC Characteristics** **Stage** **TNM Edition(s)** **Histology** **Tumor Size**	**Treatment Characteristics** **Surgical Approach** **SBRT/SABR Dosing and Frequency**
Zhao, 2017[183] Surgery N=7,989 KQ 6 Fair	SEER U.S. 2004-2012 Patients with histologically diagnosed Stage 1A lung adenocarcinoma measuring ≥10 but ≤20 mm, not confined to hilus or a primary tumor in main bronchus, and treated with segmentectomy or lobectomy, but not post-operative radiotherapy Followup, median 52.2 mos Funding source Government, university	Age, mean (SD) S: 69.8 yrs (9.2 yrs) L: 67.3 yrs (9.6 yrs) Male, N (%) <u>Female</u> Total: *3,184 (39.9)* S: *202 (35.8)* L: *2,982 (40.2)* White, N (%) Total: *6,834 (85.5)* S: 498 (88.3) L: 6,336 (85.3) Comorbidities, N (%) NR	Stage, N (%) p-stage T1a: 7,989 (100) c-stage T1b: 7,989 (100) TNM edition(s) 8th edition Histology, N (%) <u>Major adenocarcinoma</u> Total: *7,413 (92.8)* S: 506 (89.7) L: 6,907 (93.0) <u>Mucinous adenocarcinoma</u> Total: *348 (4.4)* S: 27 (4.8) L: 321 (4.3) <u>BAC, nonmucinous</u> Total: *228 (2.9)* S: 31 (5.5) L: 197 (2.7) Tumor size, median (SD) Total: NR S: 15.6 mm (2.9 mm) L: 16.2 mm (2.9 mm)	Surgical approach, N (%) S: 564 *(7.1)* L: 7,425 *(92.9)*

***** FEV1 was not available in 13/115 SBRT patients.

† Analytical stage included the AJCC p-stage group if available; otherwise, the c-stage group was used.

Abbreviations: 3D-CRT=three-dimensional conformal radiation therapy; ASA=American Society of Anesthesiologists; BAC=broncholoalveolar carcinoma; Bi-L=bilobectomy; c-stage=clinical stage; cm=centimeter(s); CoC=Commission on Cancer; COPD=chronic obstructive pulmonary disease; DLCO=diffusing capacity of the lungs for carbon monoxide; ECOG=Eastern Cooperative Oncology Group; FEV1=forced expiratory volume in one second; fx=fraction(s); Gy=Gray; IQR=interquartile range; JCOG=Japan Clinical Oncology Group; KQ=Key Question; L=lobectomy; N=number of patients enrolled or analyzed; NA=not applicable; NCDB=National Cancer Database; NCI=National Cancer Institute; NOS=not otherwise specified; NPC=not pathologically confirmed; NR=not reported; NSCLC=non-small cell lung cancer; p-stage=pathologic stage; PC=pathologically confirmed; S=segmentectomy; SBRT/SABR=stereotactic body radiotherapy/stereotactic ablative radiotherapy; SD=standard deviation; SEER=Surveillance, Epidemiology, and End Results Program; SLR=sublobar resection; STS-GTS=Society of Thoracic Surgeons-General Thoracic Surgery Database; surg exp=surgical experience; T=thoracotomy; TNM=tumor-node-metastasis cancer staging system; U.K.=United Kingdom; U.S.=United States; VATS=video-assisted thoracoscopic lobectomy; VMAT=volumetric modulated arc therapy; VPI=visceral pleural invasion; W=wedge resection.

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Brunelli, 2015[181] N=1,370 (1,370) KQs 6, 7 Good	5-yr OS ThRCRI prognostic class A (score 0 to 1) Total: 66 (NR) p-stage T1: 73 (NR) p-stage T2: 61 (NR) ThRCRI prognostic class B (score 1.5 to 2.5) Total: 53 (NR) p-stage T1: 64 (NR) p-stage T2: 48 (NR) ThRCRI prognostic class C (score >2.5) Total: 35 (NR) p-stage T1: 55 (NR) p-stage T2: 32 (NR)	5-yr LCSS ThRCRI prognostic class A (score 0 to 1) Total: 77 (NR) ThRCRI prognostic class B (score 1.5 to 2.5) Total: 75 (NR) ThRCRI prognostic class C (score >2.5) Total: 55 (NR)	30-day mortality 24 (1.8) Postoperative cardiac-related mortality, % ThRCRI prognostic class A (score 0 to 1) Total: 0.03 ThRCRI prognostic class B (score 1.5 to 2.5) Total: 1.4 ThRCRI prognostic class C (score >2.5) Total: 4.1	Major postoperative cardiac events in hospital or within 30 days of surgery (i.e., acute MI, pulmonary edema, ventricular fibrillation or primary cardiac arrest, complete heart block, any cardiac-related death) Total sample 80 (5.8) ThRCRI prognostic class A (score 0 to 1), % Total: 11 ThRCRI prognostic class B (score 1.5 to 2.5), % Total: 19 ThRCRI prognostic class C (score >2.5), % Total: 42 Major postoperative cardiac morbidity, % ThRCRI prognostic class A (score 0 to 1) Total: 4 ThRCRI prognostic class B (score 1.5 to 2.5) Total: 11 ThRCRI prognostic class C (score >2.5) Total: 17 Cardiac event mortality during followup, % ThRCRI prognostic class A (score 0 to 1) Total: 1.5 ThRCRI prognostic class B (score 1.5 to 2.5) Total: 7 ThRCRI prognostic class C (score >2.5) Total: 13

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Bryant, 2018[196] N=*3,620* for surgery (total=*3,620*; L=2,986; SLR=634) KQs 6, 7 Fair	5-yr OS L: 70 (NR) SLR: 56 (NR) 5-yr LC mortality L: 23 (NR) SLR: 32 (NR)	NR	30-day mortality L: *57* (1.9) SLR: *11* (1.7) 90-day mortality L: *107* (3.6) SLR: *16* (2.5)	NR
Chang, 2007[192] N=10,761 (total=10,761; L=8,527; SLR=2,234) KQ 6 Fair	5-yr OS All surg: 57.8 (NR) L: 61.4 (NR) SLR: 44.0 (NR) 5-yr OS after all surgeries and stratified by gender Female: 63.0 (NR) Male: 52.8 (NR) p<0.0001 5-yr OS after all surgeries and stratified by age Age <67: 65.2 (NR) Age ≥67: 51.5 (NR) p<0.0001	NR	NR	NR
Cox, 2017[186] N=1,991 (total=1,991; L=1,544; SLR=447) KQ 6 Fair	5-yr OS Total: NR L: 70.5 (NR) SLR: 67.8 (NR)	NR	NR	NR
Fernandez, 2012[188] N=657 (657) KQ 6 Fair	Unadjusted 5-yr OS 41 (NR) Unadjusted 5-yr DSS 59 (NR)	NR	NR	NR

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Goya, 2005[195] N=*3,965* eligible (total=3,965; c-stage 1A=2,423 and 1B=1,542; p-stage 1A=2,009 and 1B=1,418) KQ 6 Fair	5-yr OS c-stage 1 IA: 72.1 (NR) IB: 49.9 (NR) p-stage 1 IA: 79.5 (NR) IB: 60.1 (NR)	NR	NR	NR
Guerrera, 2015[171] N=848 (848) KQ 6 Fair	5-yr OS 74 (0.71 to 0.77)	NR	NR	NR
Husain, 2015[239] N=112,216 (71,175) KQ 7 Fair	NR	NR	Overall 30-day mortality All surg: *1,566* (2.2) 30-day mortality – subgroup analyses stratified by comorbidities and age, % Charlson-Deyo Comorbidity Score=0 Age <75 yrs All surg: 1.3 L: 1.2	NR

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Husain, 2015[239] (continued)			SLR: 1.5 Age ≥75 yrs All surg: 3.3 L: 3.4 SLR: 3.1 Charlson-Deyo Comorbidity Score=1 Age <75 yrs All surg: 1.6 L: 1.6 SLR: 1.6 Age ≥75 yrs All surg: 4.1 L: 4.5 SLR: 2.7 Charlson-Deyo Comorbidity Score=2 Age <75 yrs All surg: 2.3 L: 2.3 SLR: 2.3 Age ≥75 yrs All surg: 5.8 L: 6.6 SLR: 3.9	
Khullar, 2015[178] N= 54,350 (54,350) KQ 6 Fair	5-yr OS c-stage 1: 57.2 (NR) p-stage 1: 60.5 (NR)	NR	NR	NR

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Khullar, 2015[189] Total N=28,241 (total=28,241; for OS: L=4,857; W=1,891; S=286; for 30-day mortality: L=19,718; W=7,297; S=1,226) KQs 6, 7 Fair	5-yr OS Total: NR L: 70.4 (69.0 to 71.7) W: 54.6 (52.3 to 56.9) S: 59.6 (53.5 to 65.2)	NR	30-day mortality Total: *445 (1.6)* L: *316* (1.6) W: *110* (1.5) S: *19* (1.6)	NR
Lakha, 2014[175] N=16,315 (15,067) KQ 6 Fair	5-yr OS Range: 53 (49 to 57) to 75 (74 to 77) <2 cm without VPI: 75 (74 to 77) <2 cm with VPI: 70 (66 to 75) 2-3 cm without VPI: 68 (65 to 70) 2-3 cm with VPI: 61 (56 to 65) >3-5 cm without VPI: 60 (57 to 62) >3-5 cm with VPI: 53 (49 to 57)	5-yr LCSS Range: 66 (62 to 69) to 88 (86 to 89) <2 cm without VPI: 88 (86 to 89) <2 cm with VPI: 84 (81 to 87) 2-3 cm without VPI: 79 (77 to 81) 2-3 cm with VPI: 71 (67 to 75) >3-5 cm without VPI: 72 (70 to 74) >3-5 cm with VPI: 66 (62 to 69)	NR	NR
Landreneau, 2014[176] N=624 (624) KQs 6, 7 Fair	5-yr OS Total: NR S: 54 (0.47 to 0.61) L: 60 (0.54 to 0.67)	NR	30-day mortality Total: *12 (1.9)* S: *4* (1.2) (95% CI, 0.4-32) L: *8* (2.5) (95% CI, 1.1 to 5.0) 90-day mortality Total: *23 (3.7)* S: *8* (2.6) (95% CI, 1.1-5.0) L: *15* (4.8) (95% CI, 2.7 to 7.8)	Overall morbidity Total: *217 (34.8)* S: *115* (36.9) L: *102* (32.7)

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Licht, 2013[249] N=1,513 (total=1,513; VATS L=717; Open L=796) KQ 7 Fair	NR	NR	30-day mortality Total: *31* (2.0) VATS L: *8* (1.1) Open L: *23* (2.9)	NR

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Louie, 2016[238] *13,598 (13,598)* KQ 7 Fair	NR	NR	30-day mortality Total: *106 (0.8)* Robotic L: *7* (0.6) VATS L: *99* (0.8) In-hospital mortality Total: *78 (0.6)* Robotic L: *4* (0.3) VATS L: *74* (0.6)	Air leak >5 days Total: 1,334 (9.8) Robotic L: 122 (10.0) VATS L: 1,212 (9.8) Adult respiratory distress syndrome Total: 61 (0.4) Robotic L: 2 (0.2) VATS L: 59 (0.5) Atelectasis requiring bronchoscopy Total: 391 (2.9) Robotic L: 31 (2.5) VATS L: 360 (2.9) Atrial arrhythmia requiring treatment Total: 1,346 (9.9) Robotic L: 125 (10.2) VATS L: 1,221 (9.9) Bronchopleural fistulas Total: 42 (0.3) Robotic L: 7 (0.6) VATS L: 35 (0.3) Chylothorax requiring medical intervention Total: 64 (0.5) Robotic L: 4 (0.3) VATS L: 60 (0.5) DVT Total: 52 (0.4) Robotic L: 5 (0.4) VATS L: 47 (0.4) Emphysema requiring treatment Total: 50 (0.4) Robotic L: 6 (0.5) VATS L: 44 (0.4) Initial ventilatory support >48 hours Total: 50 (0.4) Robotic L: 6 (0.5) VATS L: 44 (0.4)

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Louie, 2016[238] (continued)				Myocardial infarction Total: 42 (0.3) Robotic L: 5 (0.4) VATS L: 37 (0.3) Pneumonia Total: 442 (3.3) Robotic L: 33 (2.7) VATS L: 409 (3.3) Pneumothorax requiring CT reinsertion Total: 474 (3.5) Robotic L: 51 (4.2) VATS L: 423 (3.4) Pulmonary embolus Total: 62 (0.5) Robotic L: 4 (0.3) VATS L: 58 (0.5) Recurrent laryngeal nerve paresis/paralysis Total: 26 (0.2) Robotic L: 2 (0.2) VATS L: 24 (0.2) Reintubation Total: 308 (2.3) Robotic L: 25 (2.0) VATS L: 283 (2.3) Required reoperation for bleeding Total: 65 (0.9) Robotic L: 3 (0.8) VATS L: 62 (0.9) Respiratory failure Total: 119 (1.9) Robotic L: 16 (1.9) VATS L: 103 (1.9) Tracheostomy Total: 99 (0.7) Robotic L: 9 (0.7) VATS L: 90 (0.7)

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Maeda, 2010[191] N=734 (713) KQ 6 Fair	5-yr OS 85.8 (NR) 10-yr OS 71.3 (NR)	NR	NR	NR

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Maeda, 2012[184] N=1,074 (1,070 with c-stage 1A; 691 with p-stage 1A NSCLC) KQ 6 Fair	5-yr OS c-stage 1 Total: NR NR by smoking history p-stage 1 Total: NR Smoking history of pack-years ≤20 96.5 (NR) Smoking history of pack-years >20 85.9 (NR) 5-yr OS subgroup analyses Age <65: 83.3 (NR) Age >65: 76.9 (NR) Women: 85.4 (NR) Men: 74.4 (NR) Smoking history of 0 ≤ pack-years ≤ 20 85.5 (NR) Smoking history of no pack-years 85.2 (NR) Smoking history of 0 ≤ pack-years ≤10 89.2 (NR) Smoking history of 10 < pack-years ≤20 84.5 (NR) Smoking history of 20 < pack-years ≤40 73 (NR)	NR	NR	NR

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Maeda, 2012[184] (continued)	Smoking history of 40 < pack-years ≤60 69.7 (NR) Smoking history of pack-years >60 69.3 (NR) Smoking history of pack-years >20 71.1 (NR)			
Mediratta, 2014[177] N=540 (540) KQs 6, 7 Good	5-yr OS 65 (NR)	NR	Overall in-hospital mortality (duration of assessment not specified) *5 (0.9)*	NR
Melvan, 2015[243] N=127,366 (127,366) KQ 7 Fair	NR	NR	30-day mortality 2,989 *(2.4)*	NR
Nakamura, 2015[173] N=1,336 (1,016) KQ 6 Fair	5-yr OS p-stage 1A: 81.7 (NR) p-stage 1B: 62.6 (NR)	NR	NR	Intraoperative blood loss, mean (SD) p-stage 1A: 330 mL (322 mL) p-stage 1B: 415 mL (434 mL)
Okada, 2006[193] N=567 (total=567; SLR=305; L=262) KQ 6 Fair	5-yr OS, N (%) SLR: 173 (89.6) L: 158 (89.1) 5-yr DSS, N (%) SLR: 159 (85.9) L: 149 (83.4)	NR	NR	NR

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Puri, 2014[242] N=1,066 (1,066) KQs 6, 7 Fair	Median OS (used only for descriptive purposes) 8.8 yrs	NR	<u>High-risk vs. normal-risk surgery patients</u> 30-day/hospital mortality High-risk: 2 (1) Normal-risk: 14 (2); p=0.75 Respiratory failure High-risk: 7 (4) Normal-risk: 41 (5); p=0.70 Pneumonia High-risk: 9 (5) Normal-risk: 51 (6); p=0.61 Air leak >5 days High-risk: 16 (8) Normal-risk: 54 (6); p=0.36 Emphysema High-risk: 1 (0.5) Normal-risk: 3 (0.3); p=0.55 Atrial fibrillation High-risk: 25 (13) Normal-risk: 116 (13); p=1.00 Hemorrhage requiring reoperation High-risk: 2 (1) Normal-risk: 8 (1); p=1.00 Pulmonary embolism High-risk: 2 (1) Normal-risk: 3 (0.3); p=0.23 Myocardial infarction High-risk: 0 (0) Normal-risk: 5 (1); p=0.59 Stroke High-risk: 0 (0) Normal-risk: 3 (0.3); p=1.00	NR

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Puri, 2015[252] N=111,731 for surg (all surg=109,485; all surg PSM subset=5,355; all SLR=19,339; SLR PSM subset=4,555) KQ 7 Fair	NR	NR	30-day mortality All surg: 2,596/109,485 (2.4) All surg PSM subset: 136 (2.5) All SLR: 716/19,339 (3.7) SLR PSM subset: 89 (2)	NR
Razi, 2016[180] N=1,640 (1,640) KQ 6 Fair	<u>Overall sample</u> 5-yr OS L/Bi-L: 50.2 (NR) S: 43.8 (NR) W: 38.6 (NR) <u>Subset of patients with T1a tumors</u> 5-yr OS L/Bi-L: 51.8 (NR) S: 45.9 (NR) W: 43.4 (NR)	<u>Overall sample</u> 5-yr LCSS L/Bi-L: 64.5 (NR) S: 59.1 (NR) W: 52.7 (NR) <u>Subset of patients with T1a tumors</u> 5-yr LCSS L/Bi-L: 66.3 (NR) S: 61.7 (NR) W: 59 (NR)	NR	NR
Rosen, 2014[244] N=66,283 (66,283) KQ 7 Fair	NR	NR	30-day mortality *1,790* (2.7)	NR

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Rosen, 2016[185] Primary analyses (i.e., patients selected for Charlson-Deyo score=0) N=13,652 for surg (unmatched: 13,652; PSM subset: 1,781) Secondary analyses (i.e., patients unselected based on Charlson-Deyo score) N=29,032 for surg (unmatched=29,032; PSM subset=235) KQs 6, 7 Good	5-yr OS Primary PSM analysis 59 (NR) Secondary PSM analysis 58 (NR)	NR	30-day mortality Primary unmatched analysis 252 (2) Secondary unmatched analysis 667 (2) 90-day mortality Primary unmatched analysis 449 (3) Secondary unmatched analysis 1,163 (4)	NR

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Samson, 2015[240] N=55,653 (N=55,653 for unmatched analysis; 27,022 for PSM analysis; 971 for single-center analysis) KQs 6, 7 Fair	NR	NR	30-day mortality <u>PSM analysis</u> Early surg: 322 (2.4) Delayed surg: 391 (2.9) <u>Single-center analysis</u> Early surg: 6 (1.1) Delayed surg: 14 (3.1)	<u>Single-center analysis</u> Pneumonia Early surg: 33 (6) Delayed surg: 51 (11) Wound infection Early surg: 4 (1) Delayed surg: 5 (1) Blood transfusion Early surg: 18 (3) Delayed surg: 39 (9) Air leak Early surg: 59 (11) Delayed surg: 43 (10) Respiratory failure Early surg: 27 (5) Delayed surg: 44 (10) Arrhythmia Early surg: 94 (18) Delayed surg: 79 (18) DVT Early surg: 8 (2) Delayed surg: 13 (3) Myocardial infarction Early surg: 5 (1) Delayed surg: 1 (0.2) Reintubation Early surg: 23 (4) Delayed surg: 34 (8) Renal failure Early surg: 9 (2) Delayed surg: 11 (2)

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Samson, 2017[245] N=146,908 (total=146,908; nonanatomical vs. anatomical=146,908; early vs. delayed=145,090; R0 vs. ≥R1=144,921; <10 vs. ≥10 LNs=136,612) KQ 7 Fair	NR	NR	30-day mortality Nonanatomical vs. anatomical resection Nonanatomical: 491 (1.8) Anatomical: 2,158 (2.2) Between-group p <0.001 Early vs. delayed resection Early (<8 weeks): 2,000 (2.0) Delayed (≥8 weeks): 619 (2.6) Between-group p <0.001 R0 vs. ≥R1 resection R0: 2,433 (2.0) ≥R1: 163 (3.8) Between-group p <0.001 <10 vs. ≥10 lymph nodes <10 LNs obtained: 1,674 (2.1) ≥10 LNs obtained: 790 (2.3) Between-group p=0.06 90-day mortality Nonanatomical vs. anatomical resection Nonanatomical: 975 (3.6) Anatomical: 3,866 (4.0) Between-group p=0.003 Early vs. delayed resection Early (<8 weeks): 3,633 (3.7) Delayed (≥8 weeks): 1,148 (4.8) Between-group p <0.001 R0 vs. ≥R1 resection R0: 4,434 (3.8) ≥R1: 312 (7.4) Between-group p <0.001 <10 vs. ≥10 LNs <10 LNs obtained: 3,090 (3.9) ≥10 LNs obtained: 1,396 (4.0) Between-group p=0.23	NR

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Sawabata, 2011[190] N=*9,083* eligible (*9,083*) KQ 6 Fair	5-yr OS c-stage 1A: 82 (NR) c-stage 1B: 63.4 (NR) p-stage 1A: 85.9 (NR) p-stage 1B: 69.3 (NR)	NR	NR	NR
Scheel, 2015[170] All surg N=800 L patients N=638 SLR patients N=162 KQs 6, 7 Fair	5-yr OS *71.9* (NR)	NR	30-day hospital mortality – all surg patients *8 (1.0)* 30-day hospital mortality – L patients *7 (0.9)*	Any perioperative morbidity – all surg patients *220 (27.5)* Any perioperative morbidity – L patients *188 (23.5)* Specific AEs – all surg patients Pneumonia *42 (5.3)* Emphysema *3 (0.4)* Blood Transfusion *9 (1.1)* Hemorrhage Requiring Reoperation *6 (0.8)* Bronchopleural Fistula *3 (0.4)* Prolonged Air Leak *54 (6.8)* Respiratory Failure *43 (5.4)* Dysrhythmia *98 (12.3)* DVT *12 (1.5)* Renal Failure *7 (0.9)* Stroke *4 (0.5)*

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Scheel, 2015[170] (continued)				Specific AEs – L patients Pneumonia *37 (4.6)* Emphysema *3 (0.4)* Blood Transfusion *9 (1.1)* Hemorrhage Requiring Reoperation *5 (0.6)* Bronchopleural Fistula *3 (0.4)* Air Leak *43 (5.4)* Respiratory Failure *40 (5.0)* Dysrhythmia *91 (11.4)* DVT *9 (1.1)* Renal Failure *6 (0.8)* Stroke *2 (0.3)*

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Schuchert, 2012[248] Total: N=899 (total=899; S=305; L=594) Aged ≥80 yrs: N=103 (S=39, L=64) Aged 70 to 79 yrs: N=358 (S=132; L=226) Aged <70 yrs: N=439 (S=134; L=305) KQ 7 Fair	NR	NR	30-day mortality Overall: *17 (1.9)* S: *4* (1.3) L: *13* (2.2) 90-day mortality Overall: *37 (4.1)* S: *11* (3.6) L: *26* (4.4)	Overall morbidity <u>Total sample</u> Overall: *380 (42.3)* S: *109* (35.7) L: *271* (45.7) <u>Aged ≥80 yrs</u> Overall: *55 (53.0)* S: *17* (43.6) L: *38* (58.7) <u>Aged 70-79 yrs</u> Overall: *142 (39.6)* S: *48* (36.4) L: *94* (41.4) <u>Aged <70 yrs</u> Overall: *161 (36.7)* S: *45* (33.6) L: *116* (38.1) Major morbidity Overall: *111 (12.3)* S: *28* (9.2) L: *83* (14.0) Pulmonary morbidity Overall: *220 (24.5)* S: *52* (17.0) L: *168* (28.3) Estimated blood loss, median (range) Overall: NR S: 185 mL (10 to 650 mL) L: 291 mL (50 to 800 mL) Operative time, median (range) Overall: NR S: 147 mins (35 to 296 mins) L: 216 mins (40 to 381 mins)

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Shapiro, 2012[247] N=4,975 (4,975 for most outcomes; 4,645 for hospital stay outcomes) KQ 7 Fair	NR	NR	30-day mortality Total: *178* (3.6) (95% CI, 3.1 to 4.1) ≤10 LNs: 135 (3.6) >10 LNs: 43 (3.6)	Extrapulmonary infections (shock, septicemia, bacterial infection, postoperative infection, bacteremia, kidney infection, and infection-related procedure) Total: *295 (5.9)* ≤10 LNs: 220 (5.8) >10 LNs: 75 (6.3) Transfusion Total: *180 (3.6)* ≤10 LNs: 143 (3.8) >10 LNs: 37 (3.1) 30-day readmission Total: *380 (7.6)* ≤10 LNs: 301 (8.0) >10 LNs: 79 (6.6) Prolonged LOS Total: *808 (16.2)* ≤10 LNs: 633 (18.0) >10 LNs: 175 (5.5) Postoperative ICU stay Total: *3,390 (68.1)* ≤10 LNs: 2,547 (72.4) >10 LNs: 843 (74.9) Cardiovascular complications (acute MI and acute coronary occlusion without MI) Total: *82 (1.6)* ≤10 LNs: 64 (1.7) >10 LNs: 18 (1.5)

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Shapiro, 2012[247] (continued)				Thromboembolic complications (DVT and pulmonary embolism) Total: *98 (2)* ≤10 LNs: 64 (1.7) >10 LNs: 34 (2.8) Respiratory complications (adult respiratory distress syndrome, respiratory failure, bronchitis, pneumonia, empyema, abscess of lung, abscess of mediastinum and respiratory infection) Total: *1,414 (28.4)* ≤10 LNs: 1,095 (29.0) >10 LNs: 319 (26.7) Reoperation (thoracotomy for postoperative complications, reoperation for emphysema, bronchial fistula repair, and hemorrhage control) Total: *73 (1.5)* ≤10 LNs: 48 (1.3) >10 LNs: 25 (2.1)
Shirvani, 2012[237] N=7,808 for surg (total=7,808; SLR=1,277; L=6,531) KQ 7 Fair	NR	NR	30-day mortality SLR: 15.32 (1.2) L: 84.90 (1.3) 90-day mortality SLR: 52.36 (4.1) L: 267.77 (4.1)	NR
Shirvani, 2014[241] N=8,711 for surg (total=8,711; L=7,215; SLR=1,496) KQ 7 Fair	NR	NR	90-day mortality L: 289 (4.0) SLR: 55 (3.7)	NR

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Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Speicher, 2016[187] N=39,403 (total=11,990; NR for L or SLR) KQ 6 Fair	5-yr OS Total: NR L: 66.2 (NR) SLR: 51.2 (NR)	NR	NR	NR
Stephens, 2014[182] N=963 (963) KQs 6, 7 Fair	5-yr OS Total: NR VATS L: 78 (NR) Open L: 68 (NR)	NR	30-day mortality Total: *10 (1.0)* VATS L: 1 *(0.3)* Open L: 9 (1) 90-day mortality Total: *19 (2.0)* VATS L: 3 (1) Open L: 16 (2)	Pneumonia Total: *72 (7.5)* VATS L: 17 (6) Open L: 55 (8) Sepsis Total: *13 (1.3)* VATS L: 3 (1) Open L: 10 (2) Bleeding Total: *10 (1.0)* VATS L: 3 (1) Open L: 7 (1) Bronchopleural fistulas Total: *2 (0.2)* VATS L: 0 (0) Open L: 2 *(0.3)* Respiratory arrest Total: *11 (1.1)* VATS L: 2 (1) Open L: 9 (1)

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Stephens, 2014[182] (continued)				Pulmonary morbidity Total: *139 (14.4)* VATS L: 29 (9) Open L: 110 (17) Overall morbidity Total: *279 (29.0)* VATS L: 59 (19) Open L: 220 *(33.5)* Atelectasis Total: *26 (2.7)* VATS L: 5 (2) Open L: 21 (3) Air leak >5 days Total: *64 (6.6)* VATS L: 13 (4) Open L: 51 (8) Tracheostomy Total: *15 (1.6)* VATS L: 3 (1) Open L: 12 (2) Reintubation Total: *25 (2.6)* VATS L: 7 (2) Open L: 18 (3) Acute respiratory distress syndrome Total: *12 (1.2)* VATS L: 3 (1) Open L: 9 (1) Myocardial infarction Total: *10 (1.0)* VATS L: 2 (1) Open L: 8 (1)

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Stephens, 2014[182] (continued)				Atrial arrhythmia Total: *168 (17.4)* VATS L: 36 (12) Open L: 132 (20) Ventricular arrhythmia Total: *4 (0.4)* VATS L: 0 (0) Open L: 4 (1) Cerebrovascular accident Total: *4 (0.4)* VATS L: 1 *(0.3)* Open L: 3 (1) Pulmonary embolism Total: *2 (0.2)* VATS L: 1 *(0.3)* Open L: 1 *(0.2)* DVT Total: 0 (0) VATS L: 0 (0) Open L: 0 (0) Emphysema Total: 3 *(0.3)* VATS L: 0 (0) Open L: 3 (1) Renal failure Total: *13 (1.3)* VATS L: 1 *(0.3)* Open L: 12 (2) Reoperation Total: *15 (1.6)* VATS L: 9 (3) Open L: 6 (1)

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Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Stephens, 2014[182] (continued)				Chest tube duration, median days (IQR) Total: NR VATS L: 2 (4) Open L: 3 (20) Operative time, median mins (IQR) Total: NR VATS L: 173 (57) Open L: 160 (57) LOS, median days (IQR) Total: NR VATS L: 4 (8) Open L: 6 (7)
Stokes, 2018[251] N=76,623 for surg (all surg=76,623; L=59,536; p=1,532; SLR=15,555) KQ 7 Fair	NR	NR	30-day mortality All surg: *1,586* (2.07) L: *1,191* (2.0) P: *120* (7.82) SLR: *275* (1.77) 30-day mortality stratified by age <u>≤55 yrs</u> All surg: 95 (0.97) L: 64 (0.8) P: 18 (5.2) SLR: 13 (0.96) <u>56 to 60 yrs</u> All surg: 83 (0.98) L: 64 (0.9) P: 12 (5.1) SLR: 7 (0.5)	NR

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Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Stokes, 2018[251] (continued)			61 to 65 yrs All surg: 160 (1.33) L: 119 (1.25) P: 19 (7.12) SLR: 22 (0.96) 66 to 70 yrs All surg: 272 (1.77) L: 207 (1.73) P: 23 (7.69) SLR: 42 (1.38) 71 to 75 yrs All surg: 352 (2.51) L: 271 (2.51) P: 24 (11.88) SLR: 57 (1.88) 76 to 80 yrs All surg: 383 (3.56) L: 283 (3.54) P: 20 (15.27) SLR: 80 (3.02) ≥81 yrs All surg: 242 (3.94) L: 185 (4.44) P: 2 (6.9) SLR: 55 (2.83) 90-day mortality All surg: *2,751* (3.59) L: *2,060* (3.46) P: *182* (11.86) SLR: *509* (3.27)	

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Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Stokes, 2018[251] (continued)			90-day mortality stratified by age <u>≤55 yrs</u> All surg: 152 (1.55) L: 108 (1.33) P: 28 (8.12) SLR: 16 (1.19) <u>56 to 60 yrs</u> All surg: 145 (1.71) L: 106 (1.53) P: 20 (8.47) SLR: 19 (1.47) <u>61 to 65 yrs</u> All surg: 278 (2.3) L: 211 (2.22) P: 29 (10.86) SLR: 38 (1.67) <u>66 to 70 yrs</u> All surg: 471 (3.07) L: 354 (2.95) P: 33 (11.04) SLR: 84 (2.76) <u>71 to 75 yrs</u> All surg: 626 (4.46) L: 486 (4.5) P: 35 (17.33) SLR: 105 (3.46) <u>76 to 80 yrs</u> All surg: 629 (5.85) L: 462 (5.79) P: 32 (24.43) SLR: 135 (5.1) <u>≥81 yrs</u> All surg: 448 (7.3) L: 333 (8.0) P: 2 (6.9) SLR: 113 (5.81)	

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Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Strand, 2006[194] N=1,375 eligible (total=1,375; Stage 1A=559; stage 1B=816) KQ 6 Good	5-yr OS Total: 50.8 (NR) Stage 1A: 63.5 (NR) Stage 1B: 42.1 (NR)	NR	NR	NR
Su, 2014[174] N=578 (578 for OS, 542 for DFS) – T1 patients only KQ 6 Fair	5-yr OS 72 (68 to 76)	5-yr DFS 77 (73 to 81)	NR	NR
Tsutani, 2014[179] N=618 (325 with N0 status only) KQs 6, 7 Good	N0 patients only 5-yr OS 95.9 (NR)	NR	No 30-day mortality	NR

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Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Valle, 2016[246] Surg N=1,183 *(1,067* for perioperative death, 1,033 for acute toxicity) KQ 7 Fair	NR	NR	30-day mortality 16 (1.5)	Any acute toxicity (within 60 days of surg) 241 (23) reporting 381 toxicity events Pneumonia (infectious) *41* (4) Hemoptysis 0 (0) Respiratory failure *31* (3) Home oxygen *93* (9) Pleural effusion (nonmalignant) *62* (6) Pneumothorax *41* (4) ICU admission *31* (3) Dyspnea requiring hospitalization *10* (1) Hospitalization (other) *31* (3)
Yang, 2016[250] N=20,191 (for open L vs. MIS L analysis: total=18,780; open L=9,390; MIS L=9,390; for VATS L vs. robotic L analysis: total=3,876; VATS L=1,938; robotic L=1,938) KQ 7 Fair	NR	NR	30-day mortality <u>Open vs. MIS analysis</u> Open L: 117 (1.8) MIS L: 79 (1.5) <u>VATS vs. robotic analysis</u> VATS L: 17 (1.5) Robotic L: 12 (1.3) 30-day readmission <u>Open vs. MIS analysis</u> Open L: 375 (4) MIS L: 467 (5) <u>VATS vs. robotic analysis</u> VATS L: 103 (5.3) Robotic L: 89 (4.6) Conversion from MIS to open procedure <u>VATS vs. robotic analysis</u> VATS L: 340 (17.5) Robotic L: 200 (10.3)	NR

Appendix E Table 5. KQs 6 and 7: Surgery Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes, % (95% CI)*	Long-Term Progression-Related Outcomes, % (95% CI)*	Short-Term Mortality, N (%)*	Adverse Events, N (%)*
Zhai, 2014[172] N=724 (subset of sample with Stage 1 NSCLC) KQ 6 Fair	5-yr OS Total: 73.7 (NR) COPD: 72.8 (NR) No COPD: 74.0 (NR)	NR	NR	NR
Zhao, 2017[183] N=7,989 (total=7,989; S=564; L=7,425) KQ 6 Fair	5-yr OS Total: NR S: 69.0 (NR) L: 70.7 (NR)	5-yr LCSS Total: NR S: 81.3 (NR) L: 83.6 (NR)	NR	NR

* Unless otherwise specified.

Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary disease; DSS=disease-specific survival; DVT=deep vein thrombosis; ICU=intensive care unit; KQs=key questions; L/Bi-L=bilobectomy; LC=lung cancer; LNs=lymph node; MI=myocardial infarction; N=number; NR=not reported; NSCLC=non-small cell lung cancer; OS=overall survival; PSM=propensity score-matched; R0 resection=resection for cure or complete remission; R1= microscopic residual disease; SD=standard deviation; SLR=sublobar resection; surg=surgery; ThRCRI=Thoracic Revised Cardiac Risk Index; VATS=video-assisted thoracoscopic surgery; VPI= visceral pleural invasion; vs=versus; yr=year.

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Allibhai, 2013[259] N=185 (185) KQ 7 Fair	NR	NR	NR	Radiation pneumonitis of any grade *18 (8.2)* Grade ≥2 radiation pneumonitis *15 (8.2)* Grade 3 radiation pneumonitis *3* (1.8) No Grade 4 or 5 radiation toxicities	NR
Arnold, 2017[199] N=127 (127) KQ 6 Fair	5-yr OS, % (95% CI) 20.4 (NR)	NR	NR	NR	NR
Badellino, 2017[270] N=148 (148) KQ 7 Fair	NR	NR	NR	RTOG grade ≥3 radiation pneumonitis SBRT 3D-CRT: *4* (3.8) SBRT VMAT: *1* (2.1)	NR
Bibault, 2015[254] N=205 (total=205; Monte Carlo dose calculation protocol=88; Type A dose calculation algorithm=117) KQ 7 Fair	NR	NR	NR	Radiation pneumonitis 14 (6.8) Death during followup 24 (12)	Lung fibrosis 56 *(27.0)* Rib fracture 2 *(1.0)*

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Brooks, 2017[204] N=772 (772) KQs 6, 7 Fair	5-yr OS, % (95% CI) <75 yrs: 51.5 (NR) ≥75 yrs: 39.5 (NR)	5-yr TTP, % (95% CI) <75 yrs: 69.7 (NR) ≥75 yrs: 66.9 (NR)	NR	Radiation Toxicities Fatigue: *48 (6.2)* Dermatitis: *16 (2.1)* Esophagitis: *7 (0.9)* Pneumonitis: *36 (4.7)* Chest wall pain: *31 (4.0)* Hemoptysis: *1 (0.1)* Brachial plexopathy: *1 (0.1)* Rib fracture: *17 (2.2)* Severity of toxicity measured with CTCAE v4.0 Grade 5 toxicity Overall: *1 (0.1)* Hemoptysis: *1 (0.1)* Grade 4 toxicity: None Grade 3 toxicity Overall: NR Fatigue: 4 *(0.5)* Dermatitis: 3 *(0.4)* Pneumonitis: 7 *(0.9)* Chest wall pain: 4 *(0.5)* Grade 2 toxicity Overall: NR Fatigue: *44 (5.7)* Dermatitis: *13 (1.7)* Esophagitis: *7 (0.9)* Pneumonitis: *29 (3.7)* Chest wall pain: *27 (3.5)* Hemoptysis: *1 (0.1)* Brachial plexopathy: *1 (0.1)* Rib fracture: *17 (2.2)*	Cardiac events after SBRT *24 (3.1)*

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Bryant, 2018[196] N=3,620 for SBRT/SABR (total=3,620; L=2,986; SLR=634) KQs 6, 7 Fair	5-yr OS, % (95% CI) 44 (NR) 5-yr cancer-specific mortality, N (%) *202* (45)	NR	30-day mortality, N (%) *2* (0.5) 90-day mortality, N (%) *6* (1.4) 90-day mortality stratified by age, N (%) ≤55 yrs 7 (2.9) 56 to 60 yrs, N (%) 8 (1.92) 61 to 65 yrs, N (%) 19 (2.38) 66 to 70 yrs, N (%) 33 (2.58) 71 to 75 yrs, N (%) 38 (2.44) 76 to 80 yrs, N (%) 56 (3.26) ≥81 yrs, N (%) 80 (3.63)	NR	NR

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Crabtree, 2013[265] Timmerman, 2010[272] N=55 (55) KQ 7 Fair	NR	NR	None	Protocol-specified AEs related to treatment (grade 3 measures of lung injury, esophageal injury, heart injury, and nerve damage, and any grade 4-5 toxicity related to treatment) FEV1: *2 (3.6)* Hypocalcemia: *1 (1.8)* Hypoxia: *2 (3.6)* Pneumonitis NOS: *2 (3.6)* Pulmonary function test decreased NOS: *4 (7.3)* Maximum for protocol: *4 (7.3)* Grade 3 AEs: 7 (12.7) (95% CI, 9.6 to 15.8) Grade 3+ AEs at 30 days: 5 (9.1) Grade 3+ AEs at 90 days: 12 (21.8) Grade 4 AEs: 2 (3.6) (95% CI, 2.7 to 4.5) No grade 5 treatment-related AEs reported Additional patients with AEs attributable to SBRT but not classified prospectively as protocol-specified: 6 (10.9) (95% CI, 8.2 to 13.6)	AEs related (or not) to treatment Overall: *45 (81.8)* Blood or bone marrow: *6 (10.9)* Cardiovascular: *2 (3.6)* Constitutional symptoms: *20 (36.4)* Dermatology or skin: *7 (12.7)* GI tract: *6 (10.9)* Lymphatics: *2 (3.6)* Metabolic or laboratory: *5 (9.1)* Musculoskeletal or soft tissue: *11 (20)* Neurology: *6 (10.9)* Pain: *14 (25.5)* Pulmonary or upper respiratory tract: *33 (60)* Renal or genitourinary: *1 (1.8)* Infection: *3 (5.5)* Coagulation: *2 (3.6)* Hemorrhage or bleeding: *2 (3.6)*
Eba, 2016[201] N=40 (40) KQ 6 Fair	5-yr OS, % (95% CI) 67.0 (50.0 To 79.3)	NR	NR	NR	NR

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Ferrero, 2015[262] N=30 (30) KQ 7 Fair	NR	NR	NR	Any toxicity: 16 *(53.3)* Asthenia: 15 *(50)* Cough: 3 *(10)* Thoracic pain: 1 *(3.3)* Severity measured using RTOG scoring system Grade 1: 5 (15) Grade 2: 6 (20) Grade 3: 4 (13.3) Grade 4: 1 (3.3)	NR
Grills, 2012[256] N=483 (483) KQs 6, 7 Fair	NR	NR	NR	Grade 2 or higher pneumonitis *34* (7) Rib fracture *39* (8)	Respiratory failure 1 *(0.2)* Chronic myositis *24* (5) Grade 2 or higher dermatitis *10* (2)

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Haidar, 2014[257] N=55 (total=55; NPC=23; PC=32) KQ 7 Fair	NR	NR	NR	NPC Acute toxicity: 2 (8.7) Chronic toxicity: 3 (13) PC Acute toxicity: 4 (13) Chronic toxicity: 6 (19) NPC Acute toxicity 2 (8.7): Grade 1 hemoptysis and Grade 2 pleural effusion Chronic toxicity 3 (13): Grade 2 dyspnea, Grade 2 cough and Grade 1 pulmonary fibrosis PC Acute toxicity 4 (13): Grade 3 esophagitis, Grade 2 pneumonitis, Grade 1 cough, and Grade 1 pruritis Chronic toxicity 6 (19): Grade 2 pneumonitis, Grade 1 cough, Grade 1 pneumonitis, Grade 2 dyspnea, and Grade 2 atelectasis	NR
Jeon, 2018[268] N=53 (53) KQ 7 Fair	NR	NR	NR	Chest pain, including rib fracture: 5 (9.4) Rib fracture: *2 (3.8)* Dyspnea: *6 (11.3)* Grade 1 Overall: 5 (9.4) Chest pain, including rib fracture: 5 (9.4) Rib fracture: *2 (3.8)* Grade 3 Overall: 4 *(7.5)* Dyspnea: 4 *(7.5)* Grade 4 Overall: 2 *(3.8)* Dyspnea: 2 *(3.8)*	NR

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Jeppesen, 2018[203] N=136 (136) KQs 6, 7 Fair	5-yr OS, % (95% CI) 35 (NR)	NR	None	"Most common side effects were skin rash, rib fracture, cough and radiological pneumonitis/fibrosis without clinical symptoms" No acute grade 3+ toxicity	NR
Katoh, 2017[255] N=283 (283) KQs 6, 7 Fair	NR	NR	NR	Grade 2 or higher radiation pneumonitis 38 *(13.4)*	NR
Koshy, 2015[200] N=498 (498) KQ 6 Fair	5-yr OS, %, 95% CI 30 (NR)	NR	NR	NR	NR
Lam, 2018[202] N=4,454 (4,454) KQs 6, 7 Fair	Unmatched 5-yr OS, % (95% CI) 33.4 (NR)	NR	NR	NR	Unplanned readmissions within 30 days 17 (0.4)

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Lindberg, 2015[207] N=57 (57 for survival and early toxicity; 34 for late toxicity) KQs 6, 7 Fair	5-yr OS, % (95% CI) 30 (18 To 42)	5-yr LCSS, % (95% CI) 74 (59 to 89) 5-yr PFS, % (95% CI) 52 (33 to 70)	None	Early toxicity (≤36 mos) Overall: NR Atelectasis: 2 *(3.5)* Cough: *6 (10.5)* Dyspnea: *12 (21.1)* Exudate: *4 (7.0)* Fatigue: *9 (15.8)* Fibrosis: *12 (21.1)* Heart: *2 (3.5)* Lung infection: *2 (3.5)* Pain: *4 (7.0)* Pericardial effusion: 1 *(1.8)* Pneumonitis: 6 *(10.5)* Rib fracture: 2 *(3.5)* Skin and subcutaneous tissue: 5 *(8.8)* Upper airway infection: 1 *(1.8)* Late toxicity (>36 mos), N(%) Overall: NR COPD exacerbation: 2 (6) Cough: 1 (3) Dyspnea: *3 (8.8)* Exudate: 1 (3) Lung infection: 1 (3) Rib fracture: *6 (17.6)* Upper airway infection: 1 (3) Ventricle tachycardia: 1 (3) Severity of toxicity measured with CTCAE v4.0 or, for fibrosis, RTOG late toxicity scale (early=occurring within 36 mos of treatment; late=occurring after 36 mos of treatment) <u>Grade 5 toxicity</u>: None <u>Grade 3-4 early toxicity (≤36 mos)</u> Overall: NR Cough: 1 *(1.8)* Dyspnea: 3 *(5.3)* Exudate: 1 *(1.8)*	NR

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Lindberg, 2015[207] (continued)				Fatigue: 1 *(1.8)* Fibrosis: 3 *(5.3)* Heart: 1 *(1.8)* Lung infection: 1 *(1.8)* Pain: 2 *(3.5)* Pericardial effusion: 1 *(1.8)* <u>Grade 3-4 late toxicity (>36 mos) (N analyzed=34)</u> Overall: NR Dyspnea: 1 (3) Rib fracture: 1 (3) Ventricle tachycardia: 1 (3) <u>Grade 2 early toxicity (≤36 mos)</u> Overall: NR Atelectasis: 2 *(3.5)* Cough: 5 *(8.8)* Dyspnea: 9 *(15.8)* Exudate: 3 *(5.3)* Fatigue: 8 *(14.0)* Fibrosis: 9 *(15.8)* Heart: 1 *(1.8)* Lung infection: 1 *(1.8)* Pain: 2 *(3.5)* Pneumonitis: 6 *(10.5)* Rib fracture: 2 *(3.5)* Skin and subcutaneous tissue: 5 *(8.8)* Upper airway infection: 1 *(1.8)* <u>Grade 2 late toxicity (>36 mos) (N analyzed=34)</u> Overall: NR COPD exacerbation: 2 (6) Cough: 1 (3) Dyspnea: 2 (6) Exudate: 1 (3) Lung infection: 1 (3) Rib fracture: 5 *(14.7)* Upper airway infection: 1 (3)	

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Ma, 2017[269] N=155 (155) patients with 159 (159) tumors KQ 7 Fair	NR	NR	NR	Pulmonary embolism Total: 1 *(0.6)* Single-fx SBRT: 0 (0) Triple-fx SBRT: 1 *(1.1)* Severity of toxicity measured with CTCAE v4.0 Grade ≥3 pulmonary toxicity Total: 1 *(0.6)* Single-fx SBRT: 0 (0) Triple-fx SBRT: 1 *(1.1)*, a case of pulmonary embolism No Grade ≥3 pulmonary toxicity occurred within 6 months of SBRT	NR

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Mathieu, 2015[260] N=45 (45) KQ 7 Fair	NR	NR	NR	Radiation pneumonitis of any grade *2 (4.4)* Mortality due to radiation pneumonitis 1 *(2.2)* Dyspnea *4 (8.9)* Cough 1 *(2.2)* Radiation-induced rib fractures 3 (7) Pneumothorax requiring chest tube placement 2 *(4.4)* <u>Severity of toxicity measured with CTCAE v3.0</u> (acute=occurring within 4 mos of treatment; late=occurring after 4 mos of treatment) Grade 5 toxicity: Radiation pneumonitis: 1 *(2.2)* Grade 3 toxicity Overall: *4 (8.9)* Acute dyspnea: 1 *(2.2)* Late: 3 (7), of which 2 were cases of dyspnea and 1 was case of dyspnea, cough, and radiation pneumonitis Grade ≤2 toxicity (measured with CTCAE v3.0) Overall: 3 (7) Acute: 0 (0) Late radiation-induced rib fractures: 3 (7)	NR
Matsuo, 2014[198] N=115 (115) KQs 6, 7 Fair	5-yr OS, % (95% CI) 40.3 (31.1 To 49.3)	5-yr cause-specific death, % (95% CI) 33.8 (25.1 to 42.6)	NR	NR	No treatment-related deaths

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Nagata, 2015[205] N=164 (total=164; operable=64; inoperable=100) KQs 6, 7 Fair	5-yr OS, % (95% CI) Operable 54.0 (41.0 To 65.4) Inoperable 42.8 (33.0 To 52.3)	NR	NR	Grade 2 toxicities using CTCAE v3.0 Total: NR, but 17 events reported Mild symptomatic fractures: 7 *(4.1)* Chest wall pain: 3 *(1.8)* Cough: 3 *(1.8)* Chest pain: 2 *(1.2)* Brachial plexopathy: 1 *(0.6)* Dermatitis: 1 *(0.6)* Grade 3 toxicities using CTCAE v3.0 Total: *15 (8.9)* Dyspnea: *13 (7.7)* Hypoxia: *9 (5.3)* Pneumonitis: *10 (5.9)* Chest pain: *3 (1.8)* Cough: 1 *(0.6)* Grade 4 toxicities using CTCAE v3.0 Total: 2 *(1.2)* Dyspnea: 2 *(1.2)* Hypoxia: 1 *(0.6)* Pneumonitis: 1 *(0.6)*	NR

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Nyman, 2016[267] N=49 (49) KQ 7 Fair	NR	NR	NR	Esophagitis: 4 (8) Pneumonitis: *9 (18.4)* Dyspnea: *32 (65.3)* Fibrosis: *24 (49.0)* Cough: *25 (51.0)* Skin reactions: *16 (32.7)* Rib fractures: *8 (16.3)* Severity measured using CTCAE v3.0 grading system <u>Grade 1</u> Esophagitis: 4 (8) Pneumonitis: 7 (15) Dyspnea: 19 (40) Fibrosis: 20 (42) Cough: 19 (40) Skin reactions: 13 (27) Rib fractures: 6 (13) <u>Grade 2</u> Esophagitis: 0 (0) Pneumonitis: 2 (4) Dyspnea: 8 (17) Fibrosis: 4 (8) Cough: 5 (10) Skin reactions: 2 (4) Rib fractures: 2 (4) <u>Grade 3</u> Esophagitis: 0 (0) Pneumonitis: 0 (0) Dyspnea: 5 (10) Fibrosis: 0 (0) Cough: 1 (2) Skin reactions: 1 (2) Rib fractures: 0 (0) No Grade 4 or 5 toxicities	NR

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Robinson, 2013[266] N=78 (78) KQ 7 Fair	NR	NR	NR	Esophagitis: 2 *(2.6)* Pneumonitis: 6 (7.7) Brachial plexopathy: 1 *(1.3)* Pleural effusion: 1 *(1.3)* Soft-tissue necrosis: 1 *(1.3)* Chest-wall pain: 15 (19.2) Severity measured using CTCAE v4.0 grading system Grade 1 Total: *12 (15.4)* Acute: 18 *(1.3)* Late: *11 (14.1)* Grade 2 Total: *11 (14.1)* Acute: 1 *(1.3)* Late: *10 (12.8)* Grade 3 Total: *4 (5.1)* Acute: 0 (0) Late: *4 (5.1)*	NR
Rosen, 2014[258] N=79 (79) KQ 7 Fair	NR	NR	None	Chest wall pain 6 (7.6) (95% CI, 3.5 to 15.9) Rib fracture, N (%) 2 (2.5) (95% CI, 0.7 to 8.7) Significant skin reactions 3 (3.8) (95% CI, 1.3 to 10.5) No cases of life-threatening radiation pneumonitis, clinically significant pulmonary complications, necrosis, or fatal hemoptysis "All cases of rib fracture were late findings and resolved without intervention beyond topical creams and oral pain medications"	NR

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Rosen, 2016[185] Primary analyses (i.e., patients selected for Charlson-Deyo score=0) N=1,781 for SBRT/SABR (1,781 for both unmatched and PSM sets) Secondary analyses (i.e., patients unselected based on Charlson-Deyo score) N=235 for SBRT/SABR (235 for both unmatched and PSM sets) KQs 6, 7 Good	5-yr OS, % (95% CI) Primary Analysis Propensity-Matched Healthy Subset 29 (NR) Secondary Analysis Propensity-Matched Healthy Subset With SBRT Patients Refusing Surgery 40 (NR)	NR	NR	NR	NR
Shirvani, 2012[237] N=124 for SABR/SBRT (124) KQ 7 Fair	NR	NR	30-day mortality, N (%) 0 (0) 90-day mortality, N (%) *1* (0.8)	NR	NR
Shirvani, 2014[241] N=382 (382) KQ 7 Fair	NR	NR	90-day mortality, N (%) *5* (1.3)	NR	NR

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Stokes, 2018[251] N=8,216 for SBRT (8,216) KQ 7 Fair	NR	NR	30-day mortality, N (%) *60* (0.7) 30-day mortality stratified by age, N (%) <u>≤55 yrs</u> 3 (1.2) <u>56 to 60 yrs</u> 2 (0.5) <u>61 to 65 yrs</u> 3 (0.38) <u>66 to 70 yrs</u> 9 (0.7) <u>71 to 75 yrs</u> 10 (0.64) <u>76 to 80 yrs</u> 13 (0.76) <u>≥81 yrs</u> 20 (0.91) 90-day mortality, N (%) *241* (2.9) 90-day mortality stratified by age, N (%) <u>≤55 yrs</u> 7 (2.9) <u>56 to 60 yrs</u> 8 (1.92) <u>61 to 65 yrs</u> 19 (2.38)	NR	NR

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Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Stokes, 2018[251] (continued)			66 to 70 yrs 33 (2.58) 71-75 yrs 38 (2.44) 76-80 yrs 56 (3.26) ≥81 yrs 80 (3.63)		
Sun, 2017[197] N=73 (65) KQs 6, 7 Fair	5-yr OS, % (95% CI) 55.7 (49.4 To 62.0) 5-yr mortality, % (95% CI) NR 10-yr mortality, % (95% CI) NR		NR	NCI CTCAE (v. 3) Grade 1: 49 (75.4) Grade 2: 7 (10.8) Grade 3: 1 (1.5) Radiation pneumonitis, N (%) 57 *(87.7)*	Dermatitis Total: 21 *(32.3)* Grade 1: 16 (24.6) Grade 2: 3 (4.6) Grade 3: 2 (3.1) Hemoptysis Total: 1 (1.5) Grade 1: 1 (1.5) Grade 2: 0 (0) Grade 3: 0 (0) Dyspnea/shortness of breath Total: 19 *(29.2)* Grade 1: 11 (16.9) Grade 2: 8 (12.3) Grade 3: 0 (0) Fatigue Total: 9 *(13.9)* Grade 1: 7 (10.8) Grade 2: 2 (3.1) Grade 3: 0 (0) Chest wall pain Total: 23 *(35.4)* Grade 1: 15 (23.1) Grade 2: 7 (10.8) Grade 3: 1 (1.5) Rib fracture Total: 16 *(24.6)* Grade 1: 13 (20.0) Grade 2: 3 (4.6) Grade 3: 0 (0)

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Sun, 2017[197] (continued)					Brachial plexopathy Total: 5 *(7.7)* Grade 1: 3 (4.6) Grade 2: 2 (3.1) Grade 3: 0 (0)
Taremi, 2012[261] N=46 (total=46; female=24; male=22; COPD=29; diabetes=8) KQ 7 Fair	NR	NR	NR	RIBI Total: 17 (37) Female: 11 *(45.8)* with 30 fractures Male: 6 *(27.3)* with 13 fractures COPD: 11 *(37.9)* Diabetes: 2 *(25.0)* Total N of rib fractures: 41 ribs with 43 fracture sites Median time to developing a rib fracture (range) 21 mos (7 to 40 mos) <u>Chest wall pain toxicity</u> Patients without rib fractures 7 *(24)* Patients with rib fractures 14 *(82)* Patients with chest wall pain received higher dose of radiation to the ribs compared to patients without chest wall pain (62.76 Gy, range: 28.4 to 88.05 Gy vs. 47.21 Gy, range: 15.9 to 73.19 Gy; p value: 0.008).	NR

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Taremi, 2012[261] (continued)				In all patients except one (with 6 fractured ribs), pain became more stable after 6–8 months. Multivariate analysis found that D to 0.5 cc of the ribs (D0.5) and volume of rib receiving ≥25 Gy (V25) were significantly associated with RIBI Grading of chest wall pain and rib fractures using CTCAE v3.0 <u>Grade 1</u> With rib fractures 5 *(29.4)* Without rib fractures 4 *(13.8)* Radiologic fractures (denominator is total N of fracture sites) 10 *(23.3)* <u>Grade 2</u> With rib fractures 6 *(35.3)* Without rib fractures 3 *(10.3)* Radiologic fractures (based on total N of fracture sites) 19 *(44.2)* <u>Grade 3</u> With rib fractures 3 *(17.6)* Without rib fractures 0 (0) Radiologic fractures (based on total N of fracture sites) 14 *(32.5)*	

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Taremi, 2012[264] N=108 KQ 7 Fair	NR	NR	None	<u>Any acute/early toxicity (i.e., ≤3 mos after SBRT)</u> Overall N of patients with acute/early toxicity: 77 *(71.3)* Fatigue: 54 (50) Cough/dyspnea: 39 *(36.1)* Pneumonitis: 4 *(3.7)* Anorexia: 3 *(2.8)* Chest wall pain: 12 *(11.1)* Dyspepsia/dysphagia: 13 *(12)* Skin toxicity: 12 *(11.1)* <u>Any late toxicity (i.e., >3 mos after SBRT)</u> Overall N of patients with late toxicity: 74 *(68.5)* Fatigue: 38 *(35.2)* Cough/dyspnea: 43 *(39.8)* Pneumonitis: 24 *(22.2)* Chest wall pain: 16 *(14.8)* Rib fracture: 27 *(25)* Pleural effusion: 2 *(1.9)* Hemoptysis: 5 *(4.6)* Skin toxicity: 1 *(0.9)* <u>Grading of acute/early toxicities using CTCAE v3.0</u> Grade 1: Patients NR, but 102 *(74.4%)* total events Grade 2: Patients NR, but 31 *(22.6%)* total events Grade 3: 4 *(3.7)* <u>Grading of late toxicities using CTCAE v3.0</u> Grade 1: Patients NR, but 96 *(59.3%)* total events Grade 2: Patients NR, but 54 *(33.3%)* total events Grade 3: 6 *(5.6)*	NR

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Ubels, 2015[206] N=39 (39) KQs 6, 7 Fair	5-yr OS, % (95% CI) 31 (NR)	5-yr DFS, % (95% CI) 52 (NR)	Mortality during surgery, N (%) 1 *(2.6)*	Patients with grade 2-3 events (grade 1 events NR) Any acute toxicity: *27 (69.2)* Dyspnea: *15 (38.5)* Esophageal pain: 1 *(2.6)* Thoracic pain: *10 (25.6)* Coughing: *6 (15.4)* Severity of toxicity measured with CTCAE v3.0 (acute=occurring within 4 mos of treatment; late=occurring after 4 mos of treatment) Grade 5 toxicity: None Grade 4 toxicity: None Grade 3 acute toxicity Overall: 2 *(5.1)* Dyspnea: 1 *(2.6)* Thoracic pain: 1 *(2.6)* Grade 3 late toxicity Overall: 4 *(10.3)* Dyspnea: 2 *(5.1)* Thoracic pain: 2 *(5.1)* Grade 2 acute toxicity Overall: 12 *(30.8)* Dyspnea: 6 *(15.4)* Esophageal pain: 1 *(2.6)* Thoracic pain: 1 *(2.6)* Coughing: 4 *(10.3)* Grade 2 late toxicity Overall: 14 *(35.9)* Dyspnea: 6 *(15.4)* Thoracic pain: 6 *(15.4)* Chronic cough: 2 *(5.1)*	NR

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Valle, 2016[246] N=*184* (*176* for perioperative death, *148* for acute toxicity) KQ 7 Fair	30-day mortality 3 (1.7)	NR	NR	Any acute toxicity (i.e., within 180 days of treatment completion): 34 (23) reporting 60 toxicity events Radiation pneumonitis: *13* (9) Home oxygen: *4* (3) Pleural effusion (nonmalignant): *4* (3) Pneumonia (infectious): *15* (10) Pneumothorax: 0 (0) ICU admission: 0 (0) Respiratory failure: *2* (1) Dyspnea requiring hospitalization: *4* (3) Hemoptysis: *3* (2) Hospitalization (other): *6* (4)	NR
Videtic, 2014[271] N=80 (80) KQ 7 Fair	NR	NR	NR	<u>Patients experiencing any toxicity</u> Single-fx SBRT at 30 Gy: *4 (7.3)* Single-fx SBRT at 34 Gy: *4 (16)* <u>Chest wall pain/neuropathy</u> Single-fx SBRT at 30 Gy: *2 (3.6)* Single-fx SBRT at 34 Gy: *4 (16)* <u>Pneumonitis</u> Single-fx SBRT at 30 Gy: *2 (3.6)* Single-fx SBRT at 34 Gy: 0 (0) <u>Grade 1 toxicity</u> Single-fx SBRT at 30 Gy: 0 (0) Single-fx SBRT at 34 Gy: *1 (4)* <u>Grade 2 toxicity</u> Single-fx SBRT at 30 Gy: *4 (7.3)* Single-fx SBRT at 34 Gy: *3 (12)*	NR
Videtic, 2015[263] N=84 (84) KQ 7 Fair	NR	NR	30-day mortality, N (%) SBRT at any dose: 1 *(1.2)* SBRT 34 Gy x 1 fx: 1 *(2.6)* SBRT 48 Gy x 4 fx: 0 (0)	<u>Rates of prespecified grade 3 or higher toxicities at 1 year</u> SBRT at any dose: *10 (11.9)* SBRT 34 Gy x 1 fx: 4 (10.3) (95% CI, 2.9 to 24.2) SBRT 48 Gy x 4 fx: 6 (13.3) (95% CI, 5.1 to 26.8)	<u>Respiratory failure leading to death, possibly related to SBRT</u> SBRT at any dose: 1 *(1.2)* SBRT 34 Gy x 1 fx: 0 (0) SBRT 48 Gy x 4 fx: 1 *(2.2)*

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Videtic, 2015[263] (continued)				Fatigue/malaise SBRT at any dose: *11 (13.1)* SBRT 34 Gy x 1 fx: 6 (15) SBRT 48 Gy x 4 fx: 5 (11) Musculoskeletal disorders (including pain) SBRT at any dose: *11 (13.1)* SBRT 34 Gy x 1 fx: 8 (21) SBRT 48 Gy x 4 fx: 3 (7) Injury (including fracture) SBRT at any dose: *8 (9.5)* SBRT 34 Gy x 1 fx: 7 (18) SBRT 48 Gy x 4 fx: 1 (2) Respiratory disorders SBRT at any dose: *33 (39.3)* SBRT 34 Gy x 1 fx: 18 (46) SBRT 48 Gy x 4 fx: 15 (33) Adverse changes in DLCO SBRT at any dose: *6 (7.1)* SBRT 34 Gy x 1 fx: 4 *(10.3)* SBRT 48 Gy x 4 fx: 2 *(4.4)* Adverse changes in FVC SBRT at any dose: 1 *(1.2)* SBRT 34 Gy x 1 fx: 0 (0) SBRT 48 Gy x 4 fx: 1 *(2.2)* Pneumonitis SBRT at any dose: 2 *(2.4)* SBRT 34 Gy x 1 fx: 0 (0) SBRT 48 Gy x 4 fx: 2 *(4.4)* General disorder leading to death, but possibly unrelated to SBRT SBRT at any dose: 1 *(1.2)* SBRT 34 Gy x 1 fx: 1 *(2.6)* SBRT 48 Gy x 4 fx: 0 (0)	

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Videtic, 2015[263] (continued)				Respiratory failure leading to death, possibly related to SBRT SBRT at any dose: 1 *(1.2)* SBRT 34 Gy x 1 fx: 0 (0) SBRT 48 Gy x 4 fx: 1 *(2.2)* Severity measured using CTCAE v4.0 grading system Grade 1 fatigue/malaise SBRT at any dose: *7 (8.3)* SBRT 34 Gy x 1 fx: 2 (5) SBRT 48 Gy x 4 fx: 5 (11) Grade 1 musculoskeletal disorders (including pain) SBRT at any dose: *8 (9.5)* SBRT 34 Gy x 1 fx: 5 (13) SBRT 48 Gy x 4 fx: 3 (7) Grade 1 injury (including fracture) SBRT at any dose: 4 *(4.8)* SBRT 34 Gy x 1 fx: 4 (10) SBRT 48 Gy x 4 fx: 0 (0) Grade 1 respiratory disorders SBRT at any dose: *21 (25)* SBRT 34 Gy x 1 fx: 13 (33) SBRT 48 Gy x 4 fx: 8 (18) Grade 2 fatigue/malaise SBRT at any dose: *4 (4.8)* SBRT 34 Gy x 1 fx: 4 (10) SBRT 48 Gy x 4 fx: 0 (0) Grade 2 musculoskeletal disorders (including pain) SBRT at any dose: 3 *(3.6)* SBRT 34 Gy x 1 fx: 3 (8) SBRT 48 Gy x 4 fx: 0 (0)	

Appendix E Table 6. KQs 6 and 7: SBRT Results

Study Identifiers Author, Year N Enrolled (Analyzed) KQs Addressed Quality	Long-Term Survival and Mortality Outcomes	Long-Term Progression-Related Outcomes	Short-Term Mortality	Radiation Toxicities Rib Fractures Radiation Pneumonitis, N (%) Patients* Rib Fracture, N (%) Patients*	Other Adverse Events Specific Outcome, N (%) Patients*
Videtic, 2015[263] (continued)				Grade 2 injury (including fracture) SBRT at any dose: *4 (4.8)* SBRT 34 Gy x 1 fx: 3 (8) SBRT 48 Gy x 4 fx: 1 (2) Grade 2 respiratory disorders SBRT at any dose: *7 (8.3)* SBRT 34 Gy x 1 fx: 5 (13) SBRT 48 Gy x 4 fx: 2 (4) Grade 3 SBRT at any dose: *9 (10.7)* SBRT 34 Gy x 1 fx: 4 *(10.3)* SBRT 48 Gy x 4 fx: *5 (11.1)* Grade 5 SBRT at any dose: *2 (2.4)* SBRT 34 Gy x 1 fx: 1 *(2.6)* SBRT 48 Gy x 4 fx: 1 *(2.2)*	

* Unless otherwise specified.

Abbreviations: 3D-CRT=three-dimensional conformal radiation therapy; 95% CI=95% confidence interval; AE(s)=adverse event(s); cc=cubic centimeters; COPD=chronic obstructive pulmonary disease; CTCAE=Common Terminology Criteria for Adverse Events; FVC=forced vital capacity; fx=fraction(s); D0.5=dose to 0.5 cc of the ribs; DVT=deep vein thrombosis; Gy=Gray; ICU=intensive care unit; IQR=interquartile range; LC=lung cancer; LN(s)=lymph node(s); LOS=length of stay; MI=myocardial infarction; N=number; NCI=National Cancer Institute; NR=not reported; OS=overall survival; PSM=propensity score matching (or matched); RIBI=radiation-induced bone injury; RTOG=Radiation Therapy Oncology Group; SBRT/SABR=stereotactic body radiotherapy/stereotactic ablative radiotherapy; SD=standard deviation; SLR=sublobar resection; surg=surgery; ThRCRI=Thoracic Revised Cardiac Risk Index; TTP=time-to-progression; V25=volume of rib receiving ≥25 Gy; VATS=video-assisted thoracoscopic lobectomy; VMAT=volumetric modulated arc therapy; VPI=visceral pleural invasion; vs.=versus.

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Ackerson, 2018[295] SBRT N=70 KQ 7 Fair	NA United States 2007-2014 Followup: 65 mos.	Age: 74 (IQR 69 to 79) Female: 35 (50) Race/Ethnicity: NR Smoking Status: Never: 2 (2.9) Current: 14 (20) Past: 54 (77) Comorbidities: 89% of SBRT patients were deemed medically inoperable prior to treatment Charlson Comorbidity Index: Mean (SD): 3.7 (1.4) Median (IQR): 3 (3 to 5)	Clinical T-Stage T1a: 25 (36) T1b: 29 (41) T2a: 15 (21) T2b: 1 (1) Histology: NR SBRT Dosing and Frequency: SBRT was given every 48-72 hours using 3-5 fractions. Overall, 34 (49%) patients received 12–12.5 Gy x 4; 24 (34%) patients received 18–20 Gy × 3; and 8 (11%) patients received 10 Gy × 5. Less common fractionation schemes were used to treat 4 (6%) patients.

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Baine, 2019[232] SBRT N=26,725 KQs 6 & 7 Fair	NCDB United States 2004-2014 Followup: 26.7 mos.	Age: 75 (IQR 69 to 81) Female: 14,265 (53.4) Race/Ethnicity White: 23,861 (89.3) Black: 2,230 (8.3) Indian: 76 (0.3) Pacific Islander: 258 (1.0) Other: 72 (0.3) Missing: 228 (0.9) Smoking Status: NR Comorbidities Charlson-Deyo Comorbidity Score, N (%) 0-2: 25,485 (95.4) ≥3: 1,240 (4.6)	Stage IA: 19,856 (74.3) IB: 5,659 (21.2) I NOS: 1,210 (4.5) Histology Squamous: 9,160 (34.3) Adenocarcinoma: 11,672 (43.7) NSCLC NOS: 4,457 (16.7) Other: 1,436 (5.4) SBRT Dosing, N (%) 48 Gy: 5,727 (21.4) 50 Gy: 9,677 (36.2) 54 Gy: 4,368 (16.3) 60 Gy: 6,953 (26) SBRT Fractions, N (%) 3: 7,835 (29.3) 4: 7,212 (27) 5: 9,291 (34.8) Other: 2,387 (8.9)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Ball, 2019[293] SABR N=66 KQ 7 Fair	CHISEL Australia/New Zealand Dec. 2009-June 2015 Followup: 2.6 yrs (IQR 1.6 to 3.6 yrs)	Age, Mean (SD): 74 (8) Female: 30 (45) Race/Ethnicity: NR Smoking status Current or previous smoker: 63 (97) Current smoker: 20 (31) Smoker pack-years Mean (SD): 51 (30) Median (IQR): 42 (33 to 60) Comorbidities Medically inoperable: 58 (88) Previous cancer: 28 (43) Colinet Simplified Comorbidity Score[†] Mean (SD): 10 (3) Median (IQR): 9 (8 to 11)	T Stage 1: 47 (71) 2a: 19 (29) Histology Adenocarcinoma: 32 (48) LCC: 1 (2) Mixed: 2 (3) Non-small-cell carcinoma NOS: 9 (14) SCC: 22 (33) SABR Dosing and Frequency: Overall, 8 (13%) of the 63 patients not withdrawing before treatment received 54 Gy total in 3 fractions x 18 Gy. Because their tumors were <2 cm from the chest wall, the other 55 (87%) of 63 patients received 48 Gy total in 4 fractions x 12 Gy. Treatment was initiated ideally within 4 weeks, but later than 6 weeks after, randomization.
Barriger, 2012[290] SBRT N=251 KQ 7 Fair	NA United States Feb. 2000-Oct. 2008 Followup: 17 mos. (0.3-89 mos.)	Age: 74 (45 to 100) Female: 109 (43) Race/Ethnicity: NR Smoking Status Never smoker: 6 (2) Quit >30 years: 15 (6) Quit 3 mos. to 30 years: 145 (58) Current or quit <3 months: 82 (33) Unknown: 3 (1) Comorbidities All patients were medically inoperable COPD: 192 (76) Oxygen dependent: 56 (22)	Stage IA: 138 (55) IB: 108 (43) IIB: 5 (2) Histology SCC: 76 (30) Adenocarcinoma: 70 (28) NSCLC unspecified: 105 (42) SBRT Dosing and Frequency: Median prescribed dose was 60 Gy (range: 24 to 72 Gy) delivered in 3 fractions, with a dose/fraction of 8 to 24 Gy, each separated by 2-3 days, to the 80% isodose line. Treatment time was a median of 8 days (range: 4 to 84 days).

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Baumann, 2006[227] SBRT N=141 KQs 6 & 7 Fair	NA Sweden/Denmark 1996-2003 Followup: 33 mos. (1 to 107 mos.)	Age, mean (range): 74 (56 to 90) Female: 72 (51) Race/Ethnicity: NR Smoking Status: NR Comorbidities All patients were medically inoperable COPD: 78 (55) CVD: 25 (18) COPD+CVD: 21 (15) Other malignancies: 14 (10) Other compromising diseases: 3 (2)	T Stage 1: 56 (40) 2: 85 (60) Histology SCC: 39 (28) Adenocarcinoma: 44 (31) BAC: 3 (2) NSCLC NOS: 21 (15) No histology: 34 (24) SBRT Dosing and Frequency: A total dose of 30 to 48 Gy was given in 2 to 4 fractions, with a dose/fraction of 10 to 20 Gy, generally 2 to 3 days apart.

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Berry, 2018[216] Surgery N=14,545 KQ 6 Fair	California Cancer Registry United States Jan. 2003-Dec. 2014 Followup: NR	Age at diagnosis, N (%) <60: 2401 (16.5) 60-69: 4746 (32.6) 70-79: 5450 (37.5) ≥80: 1948 (13.4) Female: 7948 (54.6) Transgender: <5 Race/Ethnicity Non-Hispanic white: 10,621 (73.0) Non-Hispanic black: 861 (5.9) Hispanic: 1,258 (8.6) Asian/Pacific Islander: 1,711 (11.8) Other/unknown: 94 (0.6) Smoking Status: NR Comorbidities: NR	c-stage 1: 14,545 (100) T Stage T1: 8305 (57.1) T2: 6202 (42.6) Unknown: 38 (0.3) Histology Adenocarcinoma: 9474 (65.1) SCC: 3227 (22.2) Large cell neuroendocrine carcinoma: 382 (2.6) Other: 964 (6.7) NSCLC NOS: 498 (3.4) Surgical Approach Lobar resection: 11,536 (79.3) SLR: 2783 (19.1) Wedge resection (SLR subtype): 2119/2783 (76.1) Segmentectomy (SLR subtype): 560/2783 (20.1) Not specified (SLR subtype): 104*/2783 (3.7*) Pneumonectomy: 226 (1.6)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Bongers, 2011[286] SABR N= 500 (530 tumors) KQ 7 Fair	NA Netherlands April 2003-April 2009 Followup: 33 mos. (13 to 86 mos.)	Age: 74 (42 to 92) Female: 209 (41.8) Race/Ethnicity: NR Smoking Status: NR Comorbidities 374 (74.8%) medically inoperable	T Stage (n=530) 1: 307 (57.9) 2: 223 (42.1) Histology (n=500) Adenocarcinoma: 61* (12.2*) SCC: 57* (11.4*) NSCLC NOS: 64* (12.8*) Not obtained: 318 (63.6) SABR Dosing and Frequency (n=530) 3 x 20 Gy: 215 (40.6) 5 x 12 Gy: 226 (42.6) 8 x 7.5 Gy: 89 (16.8)
Chang, 2012[282] SABR N=130 KQ 7 Fair	NA United States Feb. 2005-Dec. 2009 Followup: 26 mos. (6-78 mos.)	Age: 74 (48-91) Female: 63 (48.5) Race/Ethnicity: NR Smoking Status: NR Comorbidities: COPD Stage 0-II: 73 (56) COPD Stage III-IV: 57 (44) History of other type of cancer: 37 (28.5)	Stage IA: 112 (86) IB: 18 (14) Histology SCC: 36 (28) Adenocarcinoma: 58 (45) NSCLC NOS: 36 (28) SABR Dosing and Frequency: 50 Gy total, (to PTV between 75% & 90% isodose lines) administered in 4 fractions over 4 consecutive days.

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Cummings, 2018[233] SBRT N=163 KQs 6 & 7 Fair	NA United States 2007-2015 Followup 1-Fraction (SF): 24 mos. (1.6 to 64 mos) 5-Fraction (FF): 40 mos. (3 to 97 mos.)	Age: 77 (52 to 97) Female: 89* (54.6*) Race/Ethnicity: NR Pack-years smoking, years (range) SF: 50 (0 to 140) FF: 47.5 (0 to 125) Comorbidities: NR	T Stage T1b: 92 (56.4*) T1c: 34 (20.9*) NR: 37* (22.7*) Histology Adenocarcinoma: 77 (47.2*) SCC: 46 (28.2*) LCC: 1 (0.6*) BAC: 9* (5.5*) Other: 7 (4.3*) No pathology: 23* (14.1*) SBRT Dosing and Frequency: Median doses were 30 Gy in the SF arm and 50 Gy in the FF arm. In the latter, most patients received 50 Gy total in 5 fractions; 18 patients received 60 Gy total in 5 fractions.

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Detillon, 2019[231] SBRT N=378 (159 and 36 for primary and secondary PSM analyses, respectively) KQ 6 Fair	Netherlands Cancer Registry Netherlands 2010-2015 Followup Unmatched analysis: 32 mos. Primary PSM analysis: 32 mos. Secondary PSM analysis: 33 mos.	Age, Mean (SD) Unmatched analysis: 74.9 (5.9) Primary PSM analysis: 74.3 (5.4) Secondary PSM analysis: 73.5 (5.8) Female Unmatched analysis: 154 (40.7) Primary PSM analysis: 61 (38.4) Secondary PSM analysis: 14 (38.9) Race/Ethnicity: NR Smoking Status: NR Comorbidities Unmatched analysis Pulmonary: 221 (61.9) Cardiac: 158 (44.3) Hypertension: 139 (38.9) Previous malignancy: 126 (35.3) Vascular: 116 (32.5) Diabetes: 73 (20.4) Unknown: 21 (5.6) Primary PSM analysis Pulmonary: 82 (51.6) Cardiac: 67 (42.1) Hypertension: 66 (41.5) Previous malignancy: 68 (42.8) Vascular: 53 (33.3) Diabetes: 27 (17.0) Secondary PSM analysis Pulmonary: 20 (55.6) Cardiac: 14 (38.9) Hypertension: 15 (41.7) Previous malignancy: 12 (33.3) Vascular: 13 (36.1) Diabetes: 6 (16.7)	T Stage Unmatched analysis 1a: 139 (36.8) 1b: 117 (31.0) 2a: 91 (24.1) Unknown: 31 (8.2) Primary PSM analysis 1a: 49 (30.8) 1b: 53 (33.3) 2a: 57 (35.8) Secondary PSM analysis 1a: 14 (38.9) 1b: 12 (33.3) 2a: 10 (27.8) Histology Unmatched analysis Adenocarcinoma: 77 (20.4) SCC: 65 (17.2) Other: 50 (13.2) Unknown: 186 (49.2) Primary PSM analysis Adenocarcinoma: 63 (39.6) SCC: 54 (34.0) Other or unknown: 42 (26.4) Secondary PSM analysis Adenocarcinoma: 8 (22.2) SCC: 5 (13.9) Other or unknown: 23 (63.9) SBRT Dosing and Frequency: Total Gy NR, schedules varied between 3 to 8 fractions, delivered 2-3 times per week in the case of multiple fractions.

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Detillon, 2019[231] SBRT N=378 (159 and 36 for primary and secondary PSM analyses, respectively) KQ 6 Fair (continued)		N (%) of Comorbidities <u>Unmatched analysis</u> None: 9 (2.5) 1: 73 (20.5) 2: 105 (29.4) 3: 75 (21.0) ≥4: 95 (26.6) <u>Primary PSM analysis</u> None: 6 (3.8) 1: 27 (17.0) 2: 54 (34.0) 3: 34 (21.4) ≥4: 38 (23.9) <u>Secondary PSM analysis</u> None: 2 (5.6) 1: 7 (19.4) 2: 12 (33.3) 3: 8 (22.2) ≥4: 7 (19.4) Charlson Comorbidity Score, N (%) <u>Unmatched analysis</u> 0: 9 (2.5) 1: 61 (17.1) 2: 79 (22.1) 3: 83 (23.2) ≥4: 125 (35.0) <u>Primary PSM analysis</u> 0: 6 (3.8) 1: 17 (10.7) 2: 42 (26.4) 3: 40 (25.2) ≥4: 54 (34.0)	

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Detillon, 2019[231] SBRT N=378 (159 and 36 for primary and secondary PSM analyses, respectively) KQ 6 Fair (continued)		Secondary PSM analysis None: 2 (5.6) 1: 6 (16.7) 2: 10 (27.8) 3: 6 (16.7) ≥4: 12 (33.3)	
Dziedzic, 2017[217] Surgery N=6,905 KQs 6 & 7 Fair	Polish National Lung Cancer Registry Poland Jan. 2007-Dec. 2013 Followup: 36.9 mos. (95% CI, 36.1 to 37.9 mos.)	Age: 63.3 (IQR, 57.6 to 70.1) Female: 2,865 (41.5*) Race/Ethnicity: NR Smoking Status: NR Comorbidities: NR	Stage IA: 5,147* (74.5*) IB: 1,758* (25.5*) Histology Adenocarcinoma: 3,181* (46.1*) SCC: 2,235* (32.4*) Other: 1,489* (21.6*) Surgical Approach Lobectomy: 5,911 (85.6*) Segmentectomy: 233 (3.4*) Wedge resection: 761 (11*)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Ezer, 2018[273] Surgery N=9,508 KQ 7 Fair	SEER United States 2000-2009 Followup: NR	Age Total: 74.5* Open Lobectomy: 74 (5) VATS Lobectomy: 75 (6) Female Total: 5,143* (54.1*) Open Lobectomy: 4,414 (53) VATS Lobectomy: 729 (61) Race/Ethnicity White Total: 8,489* (89.3*) Open Lobectomy: 7,429 (88) VATS Lobectomy: 1,060 (89) African American Total: NR Open Lobectomy: 426 (5) VATS Lobectomy: >11 (exact N was NR) Hispanic Total: 105* (1.1*) Open Lobectomy: 94 (1) VATS Lobectomy: ≤11 (exact N was NR) Other Total: 445* (4.7*) Open Lobectomy: 374 (5) VATS Lobectomy: 71 (6) Smoking Status: NR Comorbidity score, N (%) ≤1 Total: 2,930* (30.8*) Open Lobectomy: 2,504 (30) VATS Lobectomy: 426 (36)	Stage I Total: 8,281* (87.1*) Open Lobectomy: 7,204 (87) VATS Lobectomy: 1,077 (91) Stage II Total: 1,227* (12.9*) Open Lobectomy: 1,119 (13) VATS Lobectomy: 108 (9) Histology Adenocarcinoma Total: 5,681* (59.7*) Open Lobectomy: 4,943 (60) VATS Lobectomy: 738 (62) SCC Total: 2,902* (30.5*) Open Lobectomy: 2,616 (32) VATS Lobectomy: 286 (24) LCC Total: 295* (3.1*) Open Lobectomy: 271 (3) VATS Lobectomy: 24 (2) Other Total: 630* (6.6*) Open Lobectomy: 493 (6) VATS Lobectomy: 137 (12) Surgical Approach Open Lobectomy: 8,323 (87.5*) VATS Lobectomy: 1,185 (12.5*)

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Ezer, 2018[273] Surgery N=9,508 KQ 7 Fair (continued)		1-1.5 Total: 3,081* (32.4*) Open Lobectomy: 2,679 (32) VATS Lobectomy: 402 (34) 1.5-2.5 Total: 1,125* (11.8*) Open Lobectomy: 1,029 (12) VATS Lobectomy: 96 (8) >2.5 Total: 2,372* (24.9*) Open Lobectomy: 2,111 (25) VATS Lobectomy: 261 (22)	
Factor, 2014[278] SBRT N=74 (78 tumors) KQ 7 Fair	NA United States Dec. 2006-Jul. 2012 Followup: Local control: 14.4 mos. Overall survival: 18.8 mos.	Age: 78.5 (56 to 93) Female: Patients NR, but 42 (54) tumors Race/Ethnicity: NR Smoking Status: NR Comorbidities: Patients were either medically inoperable or refused surgery	Stage IA: Patients NR, but 52 (67) tumors IB: Patients NR, but 26 (33) tumors Histology Adenocarcinoma: Patients NR, but 41 (53) tumors SCC: Patients NR, but 23 (29) tumors NSCLC NOS: Patients NR, but 10 (13) tumors Unknown: Patients NR, but 4 (5) tumors SBRT Dosing and Frequency: Median dose of 4800 cGy total, administered in 4 fractions over 4 consecutive days

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Fischer-Valuck, 2012[281] SBRT N=62 KQ 7 Fair	NA United States March 2005-Aug. 2010 Followup: 28 mos. (4 to 78 mos.)	Age, Mean (Range): 72.6 (27 to 92) Female: 35 (56.5) Race/Ethnicity: NR Smoking history: Yes: 52 (83.8) No: 10 (16.2) Comorbidities: NR	Stage IA: 44 (70.9) IB: 18 (29.1) Histology Adenocarcinoma: 22 (35.4) SCC: 22 (35.4) BAC: 3 (4.8) NSCLC NOS: 15 (24.1) SBRT Dosing and Frequency Dosing, N (%) 48 Gy (4 x 12 Gy): 13 (20.9) 60 Gy (5 x 12 Gy): 49 (79.1)
Guckenberger, 2013[280] SBRT N=582 KQ 7 Fair	NA Germany/Austria Study Years: 1998-2011 Followup, Mean: 21.4 mos	Age: 72.2 (30.9 to 92.4) Female: 177 (30.4) Race/Ethnicity: NR Smoking Status: NR Comorbidities: NR	Stage IA: 327 (56.2) IB: 236 (40.5) I (unclear): 19 (3.3) Histology Adenocarcinoma: 231 (39.7) SCC: 195 (33.5) Other: 55 (9.5) Unknown or no biopsy: 101 (1.9) SBRT Dosing and Frequency, Median (Range): N of SBRT Fractions: 3 (1 to 20) Single-fraction dose PTV-encompassing (Gy): 12.5 (2.9 to 33) Total dose PTV-encompassing (Gy): 37.5 (12 to 64)

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

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Haasbeek, 2010[291] SBRT N=193 (203 tumors) KQ 7 Fair	NA Netherlands 2003-2008 Followup: 12.6 mos. (3 to 52 mos.)	Age: 79 (57 to 91) Female: 62 (32) Race/Ethnicity: NR Smoking Status: NR Comorbidities Medically inoperable: 155 (80) COPD: 140* (72.5*)	T Stage (n=203) T1: 118 (58) T2: 85 (42) Histology (n=75) Adenocarcinoma: 23 (30.7*) SCC: 18 (24*) Undifferentiated NSCLC: 34 (45.3*) SBRT Dosing and Frequency: All patients received 60 Gy total. Half of the patients (101) received 12 Gy in 5 fractions; 69 (34%) received 20 Gy in 3 fractions; 33 (16%) received 7.5 Gy in 8 fractions.
Handa, 2018[218] Surgery N=711 KQ 6 Fair	NA Japan April 2000-Dec. 2015 Followup: 52.3 mos.	Age: NR Female: NR Race/Ethnicity: NR Smoking Status: NR Comorbidities: NR	Stage: NR Histology: NR Surgical Approach: Lobectomy or bilobectomy

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Inoue, 2013[224] SBRT N=109 KQs 6 & 7 Fair	NA Japan June 2005-Nov. 2010 Followup: 25 mos (4 to 72 mos.)	Age: 78 (47 to 90) Female: 35 (32.1*) Race/Ethnicity: NR Smoking Status: NR Comorbidities: NR	Stage (all N0M0) T1a: 47 (43.1*) T1b: 32 (29.4*) T2: 30 (27.5*) Histology Adenocarcinoma: 65 (59.6*) SCC 29 (26.6*) LCC: 1 (0.9*) NSCLC NOS: 8 (7.3*) Unproven: 6 (5.5*) SBRT Dosing and Frequency: Treatment period of 4 to 7 days 2005-2006: 48 Gy total, administered in 4 fractions 2007-2010: 40 Gy total, administered in 4 fractions to 95% volume of PTV (~45 to 50 Gy)
Jeppesen, 2013[223] SBRT N=100 KQ 6 Fair	NA Denmark Aug. 2005-June 2012 Followup: 35.4 mos. (8.8 to 90.5 mos.)	Age, Mean (Range): 73.3 (52 to 88) Female: 55 (55) Race/Ethnicity: NR Smoking Status: Smoker or ex-smoker: 81 (81) Never smoker: 19 (19) Comorbidities: All patients were medically inoperable	T-Stage T1: 72 (72) T2: 28 (28) Histology: Adenocarcinoma: 59 (59) SCC: 28 (28) Other: 13 (13) SBRT Dosing and Frequency: 15 to 22 Gy x 3, delivered in 9 days

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Karasawa, 2018[229] SABR N=56 KQs 6 & 7 Fair	NA Japan Oct. 2003-Dec. 2010 Followup: 10.6 yrs	Age: 79 (49 to 91) Female: 17 (30.4*) Race/Ethnicity: NR Smoking Status: NR Comorbidities High risk operable: 27 (48.2*) Medically inoperable: 21 (37.5*) Pulmonary risk factor: 31 (55.4*) Cardiac risk factor: 8 (14.3*) Central nervous system factor: 4 (7.1*) Hepatic risk factor: 1 (1.8*)	T Stage T1: 41 (73.2*) T2: 15 (26.8*) Histology: Adenocarcinoma: 34 (60.7*) SCC: 18 (32.1*) Large cell neuroendocrine cancer: 1 (1.8*) NSCLC NOS: 2 (3.6*) Unproven: 1 (1.8*) SBRT Dosing and Frequency: Patients primarily received 48 Gy total, delivered in 4 fractions over 1 week.
Lagerwaard, 2012[283] SABR N=382 KQ 7 Fair	NA Netherlands April 2003-Nov. 2008 Followup: 23 mos.	Age: 74 (47 to 91) Female: 152 (39.8) Race/Ethnicity: NR Smoking Status: NR Comorbidities: History of prior lung cancer: 65 (17) COPD (mild, moderate, severe, or very severe) (n=361): 304* (84*) Medically inoperable: 323 (84.6)	Stage IA: 230 (60.2) IB: 152 (39.8) Histology: NR SABR Dosing and Frequency: 60 Gy total, administered in 3, 5, or 8 fractions (depending on tumor diameter and location)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Lagerwaard, 2012[225] SABR N=177 KQs 6 & 7 Fair	NA Netherlands April 2003-Dec. 2010 Followup: 31.5 mos.	Age: 76 (50 to 91) Female: 76 (43) Race/Ethnicity: NR Smoking Status: Current or former: 168 (95) Never smoked: 9 (5) Comorbidities: COPD: 112* (63*) Charlson Comorbidity Score: Median (range): 2 (0 to 5) 0: 18 (10) 1: 59 (33) 2: 38 (22) 3: 39 (22) 4: 16 (9) 5: 7 (4)	Stage IA: 106* (60) 1B: 71* (40) Histology (n=60) Adenocarcinoma: 20 (33) SCC: 16 (27) Undifferentiated NSCLC: 24 (38) SBRT Dosing and Frequency: 60 Gy total, delivered as 20 Gy in 3 fractions for 34% of patients; 12 Gy in 5 fractions for 46%; and 7.5 Gy in 8 fractions for 19%.
Lagerwaard, 2008[292] SBRT N=206 (219 tumors) KQ 7 Fair	NA Netherlands Study Years NR Followup: 12 mos. (3 to 44 mos.)	Age: 73 (NR) Female: 91 (44) Race/Ethnicity: NR Smoking Status: NR Comorbidities Medically inoperable: 167 (81) COPD: 151* (73.3*) Previous malignancy: 80* (39) Previous lung cancer: 37 (18)	T Stage (n=219) T1: 129 (59) T2: 90 (41) Histology (n=64) Adenocarcinoma: 23 (36) SCC: 19 (30) Undifferentiated NSCLC: 22 (34 SBRT Dosing and Frequency: Total Gy NR, delivered as 20 Gy in 3 fractions for 93/219 (43%) tumors; 12 Gy in 5 fractions for 99/219 (45%); and 7.5 Gy in 8 fractions for 27 (12%).

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Lee, 2017[234] SBRT/SABR N=169 (178 tumors) KQs 6 & 7 Fair	NA South Korea June 2000-May 2015 Followup: 32 mos. (2 to 195 mos.)	Age: 73 (40 to 91) Female: 38 (22) Race/Ethnicity: NR Smoking Status: NR Comorbidities Charlson Comorbidity Index Score, median (range): 5 (0 to 8) Poor lung function: 86 (51) Other comorbidity: 27 (16)	Stage T1a: 39 (22) T1b: 70 (39) T2a: 69 (39) Histology (n=178) Adenocarcinoma: 87 (49) SCC: 78 (44) NSCLC unspecified: 5 (3) Others: 3 (2) No biopsy: 5 (3) SABR Dosing and Frequency 82 (46%) patients received 60 Gy total in 4 fractions, 51 (29%) patients received 48 Gy total in 4 fractions, 18 (10%) patients received 54 Gy total in 3 fractions, 10 (6%) patients received 60 Gy total in 3 fractions, and 17 (10%) patients received other doses/fractionations.
Liu, 2018[219] Surgical resection N=3,219 KQ 6 Fair	SEER United States 2004-2013 Followup: 37 mos. (1 to 120 mos.)	Age: 69 (20 to 92) Female: 1,918 (59.6) Race/Ethnicity: White: 2,805 (87.1) Black: 271 (8.4) Other: 143 (4.5) Smoking Status: NR Comorbidities: NR	Stage IA: 3,219 (100) Histology Adenocarcinoma: 1,892 (58.8) SCC: 738 (22.9) LCC: 142 (4.4) Other: 447 (13.9) Surgical Approach Wedge: 2,327 (72.3) Segmental: 892 (27.7)

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Lutz, 2018[220] Surgical resection N=632 KQs 6 & 7 Fair	NA France Jan. 2007-Aug. 2016 Followup, mean: 34.5	Age: 65 (IQR, 59 to 71) Female: 321 (50.8) Race/Ethnicity: NR Smoking Status: NR Comorbidities: NR	p-Stage IA: 281 (44.5) IB: 201 (31.8) IIA: 54 (8.5) IIB: 39 (6.2) IIIA: 57 (9) Histology Adenocarcinoma: 498 (78.8) SCC: 102 (16.1) LCC: 32 (5.1) Surgical Approach: All patients underwent surgical resection. The most common types of resection were right upper lobe (29.1%), segmentectomy (25.3%), and left upper lobe (15.5%).
Lv, 2018[221] Surgical resection N=861 KQ 6 Fair	SEER United States Jan. 2004-Dec. 2014 Followup: 39 mos. (0 to 131 mos.)	Age, mean (SD) Lobectomy (n=662): 65.9 (10.9) Sublobar resection (n=199): 66.6 (11.3) Female: 570* (66.2*) Race/Ethnicity White: 711* (82.6*) Black/other: 150* (17.4*) Smoking Status: NR Comorbidities: NR	Stage IA: 861 (100) Histology Adenocarcinoma: 656* (76.2*) SCC: 113* (13.1*) Other: 92* (10.7*) Surgical Approach: 662 (76.9) patients underwent lobectomy, and 199 (23.1) patients underwent sub-lobar resection.

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Manyam, 2019[230] SBRT/SABR N=139 (146 tumors) KQs 6 & 7 Fair	NA United States 2009-2016 Followup: 23.8 mos. (3.1 to 87.9 mos.)	Age: 76 (47 to 92) Female: 74 (53.2*) Race/Ethnicity: NR Smoking Status Pack-years, median (range): 50 (0 to 160) Smoking during treatment: 38 (27.5) Comorbidities Pulmonary: 80 (58) Cardiac: 12 (9) Refusal: 5 (4) Other/multifactorial: 42 (29)	Stage IA: 135 (93) IB: 10 (6) IIA: 1 (1) Histology Adenocarcinoma: 39 (27) SCC: 38 (26) Others: 8 (6) Nondiagnostic: 14 (10) No biopsy: 47 (32) SBRT Dosing and Frequency: Of 146 lesions, 80 (55%) were treated with 30 Gy and 66 (45%) were treated with 34 Gy.
Matsuo, 2012[285] SBRT N=74 KQ 7 Fair	NA Japan Sept. 2003-March 2008 Followup: 31.4 mos. (4.2 to 65.0 mos.)	Age: 77 (63 to 88) Female: 19 (25.7*) Race/Ethnicity: NR Smoking Status: NR Comorbidities: Inoperable: 50 (67.6*)	Stage T1a: 26 (35.1*) T1b: 27 (36.5*) T2a: 21 (28.4*) Histology Adenocarcinoma: 36 (48.6*) SCC: 30 (40.5*) Other (LCC or NSCLC NOS): 8 (10.8*) SBRT Dosing and Frequency: 48 Gy total, administered in 4 fractions at the isocenter; median (range) overall treatment time was 5 days (4 to 12 days)

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Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Moon, 2018[214] Surgical resection N=15,358 KQ 6 Fair	SEER United States 2000-2014 Followup: 56 mos. (IQR, 25 to 95 mos.)	Age, mean (SD) Lobectomy: 65.5 (10.2) Segmentectomy: 67.8 (10) Female: 9,037* (58.8*) Race/Ethnicity American Indian or Alaska Native: 47* (0.3*) Asian or Pacific Islander: 859* (5.6*) Black: 1,084* (7.1*) White: 13,318* (86.7*) Unknown: 50* (0.3*) Smoking Status: NR Comorbidities: NR	Stage IA: 15,358 (100) Histology Adenocarcinoma: 10,645* (69.3*) SCC: 2,881* (18.8*) Others: 1,832* (11.2*) Surgical Approach: Lobectomy: 14,549 (94.7*) Segmentectomy: 809 (5.3*)
Mutter, 2012[287] SBRT/SABR N=126 KQ 7 Fair	NA United States May 2006-July 2009 Followup: 16 mos. (3 to 43 mos.)	Age: 77 (55 to 95) Female: NR Race/Ethnicity: NR Smoking Status: NR Comorbidities: NR	Stage T1a: 63 (50*) T1b: 32 (25.4*) T2a: 27 (21.4*) Histology Adenocarcinoma: 93 (74) NSCLC unspecified: 2 (2) Not determined: 1 (1) Squamous: 30 (24) SBRT Dosing and Frequency Dose, Median (range): 54 Gy (40 to 60 Gy) Treatment time, Median (range): 7 days (4 to 19 days) Number of total fractions: 3 fractions: 73 (57.9*) 4 fractions: 38 (30.2*) 5 fractions: 15 (11.9*)

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Olsen, 2011[288] SBRT/SABR N=130 KQ 7 Fair	NA United States June 2004-June 2009 11 mos. (2 to 33 mos.)	Age: 75 (31 to 92) Female: 65* (50*) Race/Ethnicity: NR Smoking Status: NR Comorbidities: 117 of 130 patients were considered medically inoperable	Stage T1a: 56 (43.1*) T1b: 44 (33.8*) T2a: 24 (18.5*) Histology Biopsy-proven: 110* (84.6*) SBRT Dosing and Frequency 9 Gy in 5 fractions: 8 (6.2*) 10 Gy in 5 fractions: 11 (8.5*) 18 Gy in 3 fractions: 111 (85.4*)
Onishi, 2007[226] SBRT/SABR N=257 KQs 6 & 7 Fair	NA Japan April 1995-March 2004 Followup: 38 mos. (2 to 128 mos.)	Age: 74 (39 to 92) Female: NR Race/Ethnicity: NR Smoking Status: NR Comorbidities Pulmonary chronic disease: 168 (65.4*) Medically inoperable: 158 (61.5*)	Stage IA: 164 (63.8*) IB: 93 (36.2*) Histology Adenocarcinoma: 120 (46.7*) SCC: 111 (43.2*) Other: 26 (10.1*) SBRT Dosing and Frequency: 10 to 75 Gy total (at isocenter) was administered in 1 to 22 fractions.
Palma, 2010[289] SBRT/SABR N=99* KQ 7 Fair	Amsterdam Cancer Registry Netherlands 1999-2007 Followup: 54 mos.	Age: NR Female: NR Race/Ethnicity: NR Smoking Status: NR Comorbidities: NR	T Stage IA or IB: 99* (100) Histology: NR SBRT Dosing and Frequency: NR

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Sekihara, 2017[222] Surgical resection N=1,356* KQ 6 Fair	NA Japan Jan. 2002-March 2013 Followup: 40 mos.	Age: NR Female: NR Race/Ethnicity: NR Smoking Status: NR Comorbidities: NR	Pathological Stage I: 1,356* Clinical Stage I: 1,612* (78.5*) Histology: NR Surgical Approach: NR
Shibamoto, 2012[236] SBRT N=180 KQs 6 & 7 Good	NA Japan May 2004-Nov. 2008 Followup: 36 mos.	Age: 77 (29 to 92) Female: 57 (31.7*) Race/Ethnicity: NR Smoking Status: NR Comorbidities Medically inoperable: 120 (66.7*)	Stage IA: 128 (71.1*) IB: 52 (28.9*) Histology Adenocarcinoma: 104 (57.8*) SCC: 60 (33.3*) NSCLC NOS: 16 (8.9*) SBRT Dosing and Frequency 44 Gy in 4 fractions: 4 (2.2*) 48 Gy in 4 fractions: 124 (68.9*) 52 Gy in 4 fractions: 52 (28.9*) Prescribed dose was 44 Gy in 4 fractions with ≥3 day interfraction intervals (tumors with a max dimension <1.5 cm); 48 Gy in 4 fractions (tumors with a max dimension of 1.5 cm to 3.0 cm); and 52 Gy in 4 fractions (tumors with a max tumor dimension >3 cm)

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Stanic, 2014[279] SBRT N=55 KQ 7 Fair	RTOG 0236 United States Study Years: NR Followup: 2 yrs	Age: 72 (48 to 89) Female: 34 (61.8) Race/Ethnicity White: 51 (92.7) Asian: 2 (3.6) African American: 2 (3.6) Smoking Status: NR Comorbidities All patients were medically inoperable Total with >1 reason for being medically inoperable: 38 (69.1) Hypoxemia and/or hypercapnia: 10 (18.5) Severe pulmonary hypertension: 6 (10.9) Diabetes mellitus with severe end-organ damage: 3 (5.5) Severe cerebral, cardiac, or peripheral vascular disease: 24 (43.6) Severe chronic cardiac disease: 22 (40.0)	Stage IA: 44 (80) IB: 11 (20) Histology: All patients were confirmed to have NSCLC (histological details NR) SBRT Dosing and Frequency: 60 Gy total, administered in 3 fractions, separated by ≥40 hours, and the full regimen was completed within 14 days
Ueda, 2018[274] Surgical resection N=607 KQ 7 Fair	NA Japan Feb. 2008-March 2013 Followup: NR	Age Lobectomy: 67 (35 to 86) Segmentectomy: 67 (27 to 84) Female: 313* (51.6*) Race/Ethnicity: NR Smoking Status ≥40 pack years: 316* (52.1*) Comorbidities History of ischemic heart disease: 53* (8.7*) History of lung cancer resection: 36* (5.9*)	Stage IA: 607 (100) Histology: NR Surgical Approach Lobectomy: 443 (73*) Segmentectomy: 164 (27*)

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Uhlig, 2018[228] SBRT N=27,732 (1,070 in PSM analysis) KQs 6 & 7 Fair	NCDB United States 2004-2013 Followup, mean: 52.4 mos. (IQR, 32.1 to 75.2 mos.)	Age: 59 (IQR 53 to 65) Female: 601 (56.2) Race/Ethnicity African American: 55 (5.1) White: 984 (92) Other: 31 (2.9) Smoking Status: NR Comorbidities: Charlson comorbidity index score 0: 510 (47.7) 1: 335 (31.3) ≥2: 225 (21.0)	Stage I: 1,070 (100) Histology: NR SBRT Dosing and Frequency: NR for patients in PSM set, but in larger unmatched sample, the median biologic equivalent dose delivered was 100 Gy (IQR, 88 to 221 Gy). The median number of treatment sessions was 5 (IQR, 4 to 16 sessions) over a median duration of 10 days (IQR, 7 to 27 days).
Westover, 2012[284] SBRT N=15 (20 tumors) KQ 7 Fair	NA United States July 2008-Sept. 2010 Followup: 24.1 mos.	Age: 78 (62-89) Female: 12* (80*) Race/Ethnicity: NR Smoking Status: 14* (93.3*) Comorbidities COPD: 8 (53.3*) Interstitial lung disease: 1* (6.7*) History of prior lung cancer: 8* (53.3*) Systematic lupus erythematosus: 1* (6.7*)	Stage T1a: 16/20 (80) tumors T1b: 2/20 (10) tumors T2a: 2/20 (10) tumors Histology Adenocarcinoma: 9/20 (45*) tumors NSCLC NOS: 4/20 (20*) tumors SCC: 3/20 (15*) tumors No biopsy: 4/20 (20*) tumors SBRT Dosing and Frequency Median (range) total dose: 45 Gy (42-50 Gy) Median (range) fraction size: 14 Gy (10-16 Gy) 17/20 tumors (85%*) received 3 fractions

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Wink, 2019[235] SABR N=554 KQ 6 Fair	NA Netherlands/Germany 2007-2015 Followup: 36.1 mos. (1.1 to 118.3 mos.)	Age: 74 (42 to 91) Female: 234 (42.2) Race/Ethnicity: NR Smoking Status: NR Comorbidities: NR	Stage T1: 428 (77.2) T2: 124 (22.4) Histology Adenocarcinoma: 66 (11.9) SCC: 66 (11.9) LCC: 28 (5.1) AIS: 3 (0.5) NSCLC NOS: 14 (2.5) Suspicion of malignancy, but no histology: 377 (68.1) SABR Dosing and Frequency: The median prescribed dose was 54 Gy (range, 45 to 75 Gy in 3 to 8 fractions).
Ye, 2018[294] SBRT N=100 KQ 7 Fair	NA China Jan. 2010-June 2016 Followup: 26.5 mos.	Age: 73 Female: 27 (27*) Race/Ethnicity: NR Smoking Status Never: 38 (38*) Previous: 43 (43*) Current: 19 (19*) Comorbidities COPD: 55 (55*)	Stage T1: 69 (69*) T2a: 31 (31*) Histology Adenocarcinoma: 59 (59*) SCC: 22 (22*) Unknown: 19 (19*) SBRT Dosing and Frequency: Most patients received 60 Gy in 10 fractions, and the rest received 50 Gy in 5 fractions. The study's reported counts are NR here because they are incorrect.

Appendix E Table 7. KQs 6 and 7 Update Search Results: Study and Patient Characteristics

Study Identifiers Author, Year Treatment Type(s) N Enrolled KQs Addressed Quality	Study Characteristics Study or Database Name Country Study Years Followup, Median (Range)	Baseline Patient Characteristics Age, Median (Range) Gender, N (%) Race/Ethnicity, N (%) Smoking Status, N (%) Comorbidities, N (%)	NSCLC and Treatment Characteristics Stage, N (%) Histology, N (%) Surgical Approach or SBRT/SABR Dosing and Frequency
Zhou, 2017[215] Surgical resection N=20,850 KQ 6 Fair	SEER United States 2004-2013 Followup: 38 mos. (IQR, 17 to 66 mos.)	Age <60: 4,079 (19.6) 60-74: 11,112 (53.3) ≥75: 5,659 (27.1) Female: 11,339 (54.4) Race/Ethnicity White: 17,732 (85) Black: 1,665 (8) Other/unknown: 1,453 (7) Smoking Status: NR Comorbidities: NR	Stage IA1: 1,402 (6.7) IA2: 7,037 (33.8) IA3: 5,198 (24.9) IB: 7,213 (34.6) Histology Adenocarcinoma: 11,591 (55.6) SCC: 5,717 (27.4) BAC: 1,792 (8.6) Adenosquamous carcinoma: 578 (2.8) LCC: 411 (2.0) Other: 761 (3.6) Surgical Approach Lobectomy: 16,363 (78.5) Sublobar resection: 4,244 (20.4) Pneumonectomy: 243 (1.2)

*Indicates that data was calculated by abstractors

† Per the Colinet Simplified Comorbidity Score, a higher score indicates that a patient has a greater number of comorbidities.[396]

Abbreviations: AIS=adenocarcinoma in situ; BAC=bronchoalveolar carcinoma; cGy=centigray; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; ILD=interstitial lung disease; IQR=interquartile range; KQ=key question; LCC=large cell carcinoma; mos=months; NA=not applicable; NOS=not otherwise specified; NR=not reported; NSCLC=non-small cell lung cancer; PSM=propensity score matching; SABR=stereotactic ablative radiotherapy; SBRT=stereotactic body radiation therapy; SCC=squamous cell carcinoma**.**

Appendix E Table 8. KQs 6 and 7 Update Search Results: Surgery Study Outcomes

Study Identifiers Author, Year Treatment Type N Enrolled (Analyzed) KQs Addressed Quality	5-Year Survival Outcomes Overall Survival, % (95 CI) Lung Cancer Specific Survival, % (95 CI) Progression- or Recurrence-Free Survival, % (95 CI)	Short-Term Outcomes 30-Day Mortality, N (%) 90-Day Mortality, N (%) Perioperative Morbidity with ≥10% Incidence
Berry, 2018[216] Surgery N=14,545 KQ 6 Fair	Overall survival: 64.9 (95% CI, 64 to 65.8) Lung cancer-specific survival Total sample: 76.9 (95% CI, 76.1 to 77.7) SLR: 70.8 (95% CI, 68.6 to 72.9) Lobar resection: 78.5 (77.6 to 79.4) SLR vs. lobar resection: between-group p <0.0001 (both unadjusted and multivariable adjusted analyses)	NA
Dziedzic, 2017[217] Surgery N=6,905 KQs 6 & 7 Fair	Overall survival Unmatched population (n=6,905) Any resection: 76.6 (95% CI, 75.4 to 78) Wedge resection (n=761) Total: 58.1 (95% CI, 53.6 to 62.5) Stage IA: 61.3 (95% CI, 56.2 to 66.5) Stage IB: 44.8 (95% CI, 35.5 to 54.1) Lobectomy (n=5,911) Total: 79.1 (95% CI, 77.7 to 80.5) Stage IA: 80.5 (95% CI, 78.9 to 82.2) Stage IB: 75.3 (95% CI, 72.6 to 77.9) Segmentectomy (n=233) Total: 78.3 (95% CI, 70.6 to 86) Stage IA: 78 (95% CI, 68.8 to 87.1) Stage IB: 78.6 (95% CI, 64.3 to 92.9)95% CI,95% CI,95% CI,95% CI,	30-day mortality Any resection: 1.6 (95% CI, 1.3 to 1.9) Wedge resection: 1.4 (95% CI, 0.6 to 2.3) Lobectomy: 1.6 (95% CI, 1.2 to 1.9) Segmentectomy: 2.6 (95% CI, 0.5 to 4.6) 90-day mortality Any resection: 2.4 (95% CI, 2.1 to 2.8) Wedge resection: 3 (95% CI, 1.8 to 4.2) Lobectomy: 2.3 (95% CI, 1.9 to 2.7) Segmentectomy: 4.3 (95% CI, 1.7 to 6.9)
Ezer, 2018[273] Surgery N=9,508 KQ 7 Fair	NA	30-day mortality: 322* (3.4*) Respiratory complications: 3,000* (31.6*) Extended length of stay: 1,397* (14.7*)
Handa, 2018[218] Surgery N=711 KQ 6 Fair	Overall Survival: 81.3 (95% CI, NR)	NA

Appendix E Table 8. KQs 6 and 7 Update Search Results: Surgery Study Outcomes

Study Identifiers Author, Year Treatment Type N Enrolled (Analyzed) KQs Addressed Quality	5-Year Survival Outcomes Overall Survival, % (95 CI) Lung Cancer Specific Survival, % (95 CI) Progression- or Recurrence-Free Survival, % (95 CI)	Short-Term Outcomes 30-Day Mortality, N (%) 90-Day Mortality, N (%) Perioperative Morbidity with ≥10% Incidence
Liu, 2018[219] Surgical resection N=3,219 KQ 6 Fair	Lung cancer specific survival Total sample 1-6 examined LNs (n=2,410): 75 ≥7 examined LNs (n=809): 83 Wedge resection only 1-6 examined LNs (n=1,777): 74 ≥7 examined LNs (n=550): 81 Segmental only 1-6 examined LNs (n=633): 78 ≥7 examined LNs (n=259): 87	NA
Lutz, 2018[220] Surgical resection N=632 KQs 6 & 7 Fair	Overall survival Total: 75 (69.9 to 80.1) Stage IA: 79.5 (NR) Stage IB: 76.9 (NR) Lung cancer specific survival Total: 86.4 (82.3 to 90.5) Stage IA: 71.1 (NR) Stage IB: 63.6 (NR)	30-day or in-hospital mortality: 6 (0.95) Any complication: 185 (29.3)
Lv, 2018[221] Surgical resection N= 861 KQ 6 Fair	Overall survival: 75 (NR)	NA
Moon, 2018[214] Surgical resection N=15,358 KQ 6 Fair	Overall survival Lobectomy: 76.0 (75.2 to 76.8) Segmentectomy: 74.4 (95% CI, 67.7 to 75.4) Lung cancer specific survival Lobectomy: 86.0 (85.4 to 86.7) Segmentectomy: 84.7 (81.6 to 88)	NA

Appendix E Table 8. KQs 6 and 7 Update Search Results: Surgery Study Outcomes

Study Identifiers Author, Year Treatment Type N Enrolled (Analyzed) KQs Addressed Quality	5-Year Survival Outcomes Overall Survival, % (95 CI) Lung Cancer Specific Survival, % (95 CI) Progression- or Recurrence-Free Survival, % (95 CI)	Short-Term Outcomes 30-Day Mortality, N (%) 90-Day Mortality, N (%) Perioperative Morbidity with ≥10% Incidence
Sekihara, 2017[222] Surgical resection N=1,356* KQ 6 Fair	Overall survival, patients with Stage I: ILD (n=62): 44 (NR) Non-ILD (n=1,294): 84.6 (NR) Lung cancer specific survival: ILD (n=62): 56.6 (NR) Non-ILD (n=1,294): 89.8 (NR) Recurrence-free survival: ILD (n=62): 37.3 (NR) Non-ILD (n=1,294): 63.1 (NR)	NA
Ueda, 2018[274] Surgical resection N=607 KQ 7 Fair	NA	Post-operative atrial fibrillation Total: 37 (6.1*) Lobectomy (n=443): 34 (7.7*) Segmentectomy (n=164): 3 (1.8*)
Zhou, 2017[215] Surgical resection N=20,850 KQ 6 Fair	Overall death from any cause Pneumonectomy: 52.4 (44.5 to 59.2) Lobectomy: 33.0 (32.1 to 33.8) Sublobar: 47.8 (45.8 to 49.6) Cause-specific death Pneumonectomy: 34.9 (28.2 to 41.7) Lobectomy: 20.1 (19.4 to 20.9) Sublobar: 28.1 (26.5 to 29.7)	NA

*Indicates that data were calculated by abstractors.

Abbreviations: CI=confidence interval; ILD=interstitial lung disease; KQ=key question; NA=not applicable; NR=not reported; PSM=propensity score matching; SLR=sub-lobar resection.

Appendix E Table 9. KQs 6 and 7 Update Search Results: SBRT Study Outcomes

Study Identifiers Author, Year Treatment Type N Enrolled (Analyzed) KQs Addressed Quality	5-Year Survival Outcomes Overall Survival, % (95 CI) Lung Cancer Specific Survival, % (95 CI) Progression- or Recurrence-Free Survival, % (95 CI)	Short-Term Outcomes 30-Day Mortality, N (%) 90-Day Mortality, N (%) Rib Fractures, N (%) Radiation Pneumonitis, N (%) Adverse Event with ≥10% Incidence, N (%)
Ackerson, 2018[295] SBRT N=70 KQ 7 Fair	NA	30-day mortality 1 (1.4*) Adverse events Any: 12 (17) Dyspnea Total: 6 (8.6*) Grade 1: 4 (5.7*) Grade 2: 2 (2.9*) Chest Wall Toxicity: 6 (8.5)
Baine, 2019[232] SBRT N=26,725 KQs 6 & 7 Fair	Overall survival: 30.6 [95% CI, 29.9 to 31.4]	30-day mortality: 3 (0.01) 90-day mortality: 134 (0.5)
Ball, 2019[293] SABR N=66 KQ 7 Fair	NA	No treatment-related deaths occurred RP (Grades 1-2 only): 10 (18) Adverse events Grade 4: 1 (2*) Grade 3: 8* (12*) Grades 1-2 Total: 22 (39) Dyspnea: 22 (39) Cough: 33 (59) Fatigue: 32 (57) Chest wall pain: 21 (38) Pulmonary fibrosis: 22 (39) Dermatitis radiation: 6 (11) Nausea: 9 (16) Atelectasis: 9 (16) Pleural effusion: 7 (12) Fracture (type unspecified): 5 (9)

Appendix E Table 9. KQs 6 and 7 Update Search Results: SBRT Study Outcomes

Study Identifiers Author, Year Treatment Type N Enrolled (Analyzed) KQs Addressed Quality	5-Year Survival Outcomes Overall Survival, % (95 CI) Lung Cancer Specific Survival, % (95 CI) Progression- or Recurrence-Free Survival, % (95 CI)	Short-Term Outcomes 30-Day Mortality, N (%) 90-Day Mortality, N (%) Rib Fractures, N (%) Radiation Pneumonitis, N (%) Adverse Event with ≥10% Incidence, N (%)
Barriger, 2012[290] SBRT N=251 KQ 7 Fair	NA	RP Total: 42 (17) lesions Grade 4: 1 (0.4) Grade 3: 5 (2) Grade 2: 17 (7) Grade 1: 19 (8) Note: RP overall developed at a median time of 5.6 mos. (range: 0.5 to 32.2 mos.). Grade 1 RP developed at a median time of 8.4 mos. (range: 1.3 to 32.2 mos.), and symptomatic RP (Grades 2-4) developed at a median of 3.5 mos. (range: 0.5 to 12 months; p=0.002).
Baumann, 2006[227] SBRT N=141 (138 for results) KQs 6 & 7 Fair	Overall survival: 26 (95% CI, NR) Lung-cancer specific survival: 40 (95% CI, NR) Total failure-free survival: 36 (95% CI, NR)	Rib fractures: 8 (5.8*) Pneumonitis: 1 (0.7*) Any side effect: 55* (40*) Grade 3-4 toxicity: 14 (10*) Lung fibrosis: 21 (15.2*)
Bongers, 2011[286] SABR N= 500 (530 tumors) KQ 7 Fair	NA	Rib fractures (all late-onset [>3 mos. post-SABR]) (n=500): 8 (1.6) Note: Rib fractures developed at a median time of 24 mos. (range: 6 to 27 mos.) Chest wall pain (n=500 patients) Total: 57 (11.4), of which 32 (6.4) were early onset (i.e., ≤3 mos. post-SABR) and 25 (5) were late onset (i.e., >3 mos. post-SABR) Grade 3 (severe): 10 (2), of which 5 (1) were early onset and 5 (1) were late onset Grade 1-2: 47* (9.5*), of which 27 (5.4) were early onset and 20 (4.1) were late onset

Appendix E Table 9. KQs 6 and 7 Update Search Results: SBRT Study Outcomes

Study Identifiers Author, Year Treatment Type N Enrolled (Analyzed) KQs Addressed Quality	5-Year Survival Outcomes Overall Survival, % (95 CI) Lung Cancer Specific Survival, % (95 CI) Progression- or Recurrence-Free Survival, % (95 CI)	Short-Term Outcomes 30-Day Mortality, N (%) 90-Day Mortality, N (%) Rib Fractures, N (%) Radiation Pneumonitis, N (%) Adverse Event with ≥10% Incidence, N (%)
Chang, 2012[282] SABR N=130 KQ 7 Fair	NA	RP Grade 2-3: 15* (11.5*) Grade 0-1: 115* (88.5*) Adverse events Chest pain: 12 (9.3*)
Cummings, 2018[233] SBRT N=163 KQs 6 & 7 Fair	Overall survival Total: 33 (95% CI, NR) SF: 17 (95% CI, NR) FF: 39 (95% CI, NR)	RP, Grade 3: 1 (0.6*) Hospitalization Total: 9* (5.5*) SF: 3 (1.8*) FF: 6 (3.7*)
Detillon, 2019[231] SBRT N=378 (159 and 36 for primary and secondary PSM analyses, respectively) KQ 6 Fair	Overall survival Unmatched analysis: 29 (95% CI, NR) Primary PSM analysis: 29 (95% CI, NR) Secondary PSM analysis (adjusted for cT1a, histology and pathological confirmation): 49 (95% CI, NR)	NA
Factor, 2014[278] SBRT N=74 (78 tumors) KQ 7 Fair	NA	Adverse events Grade 2 RP: 1 (1.4*) No other toxicities experienced
Fischer-Valuck, 2012[281] SBRT N=62 KQ 7 Fair	NA	Rib fractures: 2 (3.2) [95% CI, 0.3 to 11.6] RP: 1 (1.6) [95% CI, 0.3 to 8.6] Adverse events Chest wall pain: 6 (9.6) [95% CI, 3.5 to 21]
Guckenberger, 2013[280] SBRT N=582 KQ 7 Fair	NA	30-day mortality: 3 (0.5) 60-day mortality: 10 (1.7) RP ≥Grade 2: 38/512 (7.4) Grade 5: 2/512 (0.4)

Appendix E Table 9. KQs 6 and 7 Update Search Results: SBRT Study Outcomes

Study Identifiers Author, Year Treatment Type N Enrolled (Analyzed) KQs Addressed Quality	5-Year Survival Outcomes Overall Survival, % (95 CI) Lung Cancer Specific Survival, % (95 CI) Progression- or Recurrence-Free Survival, % (95 CI)	Short-Term Outcomes 30-Day Mortality, N (%) 90-Day Mortality, N (%) Rib Fractures, N (%) Radiation Pneumonitis, N (%) Adverse Event with ≥10% Incidence, N (%)
Haasbeek, 2010[291] SBRT N=193 (203 tumors) KQ 7 Fair	NA	Rib fractures: 3 (1.6) RP ≥Grade 3: 4 (2.1) Adverse events in the first 3 mos. Any: 116 (60) Fatigue: 63* (32.6) Respiratory symptoms: 21* (10.9*)
Inoue, 2013[224] SBRT N=109 KQs 6 & 7 Fair	5-year overall survival Overall sample: 64 (57-80) T1a patients: 75 (58-97)	RP Grade 3: 3 (2.8) Grade 2: 15 (13.8)
Jeppesen, 2013[223] SBRT N=100 KQ 6 Fair	5-year overall survival 34 (NR) 5-year lung cancer-specific survival: 61 (NR)	No acute toxicity

Appendix E Table 9. KQs 6 and 7 Update Search Results: SBRT Study Outcomes

Study Identifiers Author, Year Treatment Type N Enrolled (Analyzed) KQs Addressed Quality	5-Year Survival Outcomes Overall Survival, % (95 CI) Lung Cancer Specific Survival, % (95 CI) Progression- or Recurrence-Free Survival, % (95 CI)	Short-Term Outcomes 30-Day Mortality, N (%) 90-Day Mortality, N (%) Rib Fractures, N (%) Radiation Pneumonitis, N (%) Adverse Event with ≥10% Incidence, N (%)
Karasawa, 2018[229] SABR N=56 KQs 6 & 7 Fair	Overall survival: 44.6 (95% CI, 31.6 to 57.7) Women had better overall survival than men, although the difference was not statistically significant (p=0.078). Women: 64.7 (95% CI, 42 to 87.4) Men: 35.9 (95% CI, 20.8 to 51) No significant difference between patients with T1 vs. T2 tumors (p=0.288). T1: 48.8 (95% CI, 33.5 to 64.1) T2: 33.3 (95% CI, 9.5 to 57.2) No significant difference between operable cases and inoperable or high-risk operable cases (p=0.466). Operable: 62.5 (95% CI, 29 to 96) High-risk operable: 44.4 (95% CI, 25.7 to 63.2) Inoperable: 38.1 (95% CI, 17.3 to 58.9) No significant difference between patients aged ≤79 yrs vs. ≥80 yrs (p=0.337). Aged ≤79 yrs: 48.4 (95% CI, 36.7 to 63.3) Aged ≥80 yrs: 40 (95% CI, 20.8 to 59.2)	Grade 3 Pulmonary toxicity: 1 (2) Cholecystitis: 1 (2) Grade 4 Stomach perforation: 1 (2)
Lagerwaard, 2012[283] SABR N=382 KQ 7 Fair	NA	Rib fracture: 4 (1) RP: Early, ≥Grade 3: 7 (1.8*) Late, ≥Grade 3: 9 (2) Adverse effects: Clinician-reported early side effects: 145* (38) Fatigue: 103* (27)

Appendix E Table 9. KQs 6 and 7 Update Search Results: SBRT Study Outcomes

Study Identifiers Author, Year Treatment Type N Enrolled (Analyzed) KQs Addressed Quality	5-Year Survival Outcomes Overall Survival, % (95 CI) Lung Cancer Specific Survival, % (95 CI) Progression- or Recurrence-Free Survival, % (95 CI)	Short-Term Outcomes 30-Day Mortality, N (%) 90-Day Mortality, N (%) Rib Fractures, N (%) Radiation Pneumonitis, N (%) Adverse Event with ≥10% Incidence, N (%)
Lagerwaard, 2012[225] SABR N=177 KQs 6 & 7 Fair	Overall survival: 51.3 (95% CI, NR)	30-day mortality: 0 (0) Rib fractures Total: 5 (3) 3-fraction scheme: 2/61 (3.3*) 5-fraction scheme: 1/82 (1.2*) 8-fraction scheme: 2/34 (5.9*) RP (Grade ≥3): 4 (2) Early side effects (Grades 1-2) Any: 103* (58*) Fatigue: 44* (25) Cough 25* (14) Local chest wall pain: 20* (11) Dyspnea: 18* (10)
Lagerwaard, 2008[292] SBRT N=206 (219 tumors) KQ 7 Fair	NA	30-day mortality: 1 (0.5*) Rib fractures: 4 (2.3*) RP (late ≥Grade 3): 6 (3) Adverse effects Any adverse effects: 101* (49*) Early side effects Fatigue: 64* (31) Local chest wall pain: 25* (12)
Lee, 2017[234] SART/SABR N=169 (178 tumors) KQs 6 & 7 Fair	Overall survival: 46.7 (NR) Cancer-specific survival: 69.4 (NR) Progression-free survival: 49.3 (NR)	Rib fractures: 39/93 (42) Rib dislocation, Grade 2: 12/93 (13) Rib fracture accompanying myositis: 8/93 (9) RP Grade 2: 19/93 (11) ≥Grade 3: 2/93 (1.2*) Radiation toxicity induced lung fibrosis: 156/169* (92) Bronchial obstruction: 19/25 (76)

Appendix E Table 9. KQs 6 and 7 Update Search Results: SBRT Study Outcomes

Study Identifiers Author, Year Treatment Type N Enrolled (Analyzed) KQs Addressed Quality	5-Year Survival Outcomes Overall Survival, % (95 CI) Lung Cancer Specific Survival, % (95 CI) Progression- or Recurrence-Free Survival, % (95 CI)	Short-Term Outcomes 30-Day Mortality, N (%) 90-Day Mortality, N (%) Rib Fractures, N (%) Radiation Pneumonitis, N (%) Adverse Event with ≥10% Incidence, N (%)
Manyam, 2019[230] SBRT/SABR N=139 (146 tumors) KQs 6 & 7 Fair	Overall survival: 28.7 (19.6 to 37.9)	Rib fracture: 7/146 (4.8) Chest wall toxicity, overall: 18/146 (12.3) Grade 1: 3/146 (2.1*) Grade 2: 13/146 (8.9*) Grade 3: 2/146 (1.4)
Matsuo, 2012[285] SBRT N=74 KQ 7 Fair	NA	Symptomatic RP Total: 15 (20.3) Grade 2: 14 (18.9*) Grade 3: 1 (1.4*)
Mutter, 2012[287] SBRT/SABR N=126 KQ 7 Fair	NA	Rib fractures: 5 (4) Chest wall pain Grade 1: 19 (15) Grade 2: 16 (13) Grade 3: 19 (15) Grade ≥2 Estimated actuarial incidence over 2 yrs: 39%
Olsen, 2011[288] SBRT/SABR N=130 KQ 7 Fair	NA	RP, Grade 2: 4 (3.1*) Chest wall toxicity: 21 (16)
Onishi, 2007[226] SBRT/SABR N=257 KQs 6 & 7 Fair	Overall survival: 47.2 (38.7 to 53.5) For operable patients (n=99): 64.8 (53.6 to 75.9) For inoperable patients (n=158): 35 (25.9 to 44.1) Lung cancer specific survival: 73.2 (66.1 to 80.2)	Rib fracture: 4 (1.6) Symptomatic radiation-induced pulmonary complications Grade >1: 28 (10.9) Grade ≥2: 14 (5.4)
Palma, 2010[289] SBRT/SABR N=99* KQ 7 Fair	NA	30-day mortality: 1* (1.0)

Appendix E Table 9. KQs 6 and 7 Update Search Results: SBRT Study Outcomes

Study Identifiers Author, Year Treatment Type N Enrolled (Analyzed) KQs Addressed Quality	5-Year Survival Outcomes Overall Survival, % (95 CI) Lung Cancer Specific Survival, % (95 CI) Progression- or Recurrence-Free Survival, % (95 CI)	Short-Term Outcomes 30-Day Mortality, N (%) 90-Day Mortality, N (%) Rib Fractures, N (%) Radiation Pneumonitis, N (%) Adverse Event with ≥10% Incidence, N (%)
Shibamoto, 2012[236] SBRT/SABR N=180 KQs 6 & 7 Good	Overall survival: 52 For operable patients (n=60): 70 For inoperable patients (n=120): 44	RP: ≥Grade 2: 24 (13.3) Grade 3: 2 (1.1)
Stanic, 2014[279] SBRT N=55 KQ 7 Fair	NA	RP Total: 9 (16.4*) Grade 1: 4 (7.3*) Grade 2: 3 (5.5*) Grade 3: 2 (3.6*) Adverse effects Pulmonary function toxicity at any time during 2-yr followup: 49 (89*) Grade 1 pulmonary/upper respiratory function toxicity: 11 (20*) Grade 2 pulmonary/upper respiratory function toxicity: 13 (23.6*) Grade 3 pulmonary/upper respiratory function toxicity: 8 (14.5*) Cough: 15* (27.3*) Dyspnea: 17* (30.9*) Pleural effusion: 5* (9.1*) Other pulmonary/upper respiratory toxicity: 7* (12.7*)
Uhlig, 2018[228] SBRT/SABR N=27,732 (1,070 in PSM analysis) KQs 6 & 7 Fair	Overall survival in PSM cohort: 26.1 (22.7 to 29.9)	30-day mortality: None 90-day mortality: None 30-day post-treatment unplanned hospital readmission rate in PSM cohort: 2 (0.2)

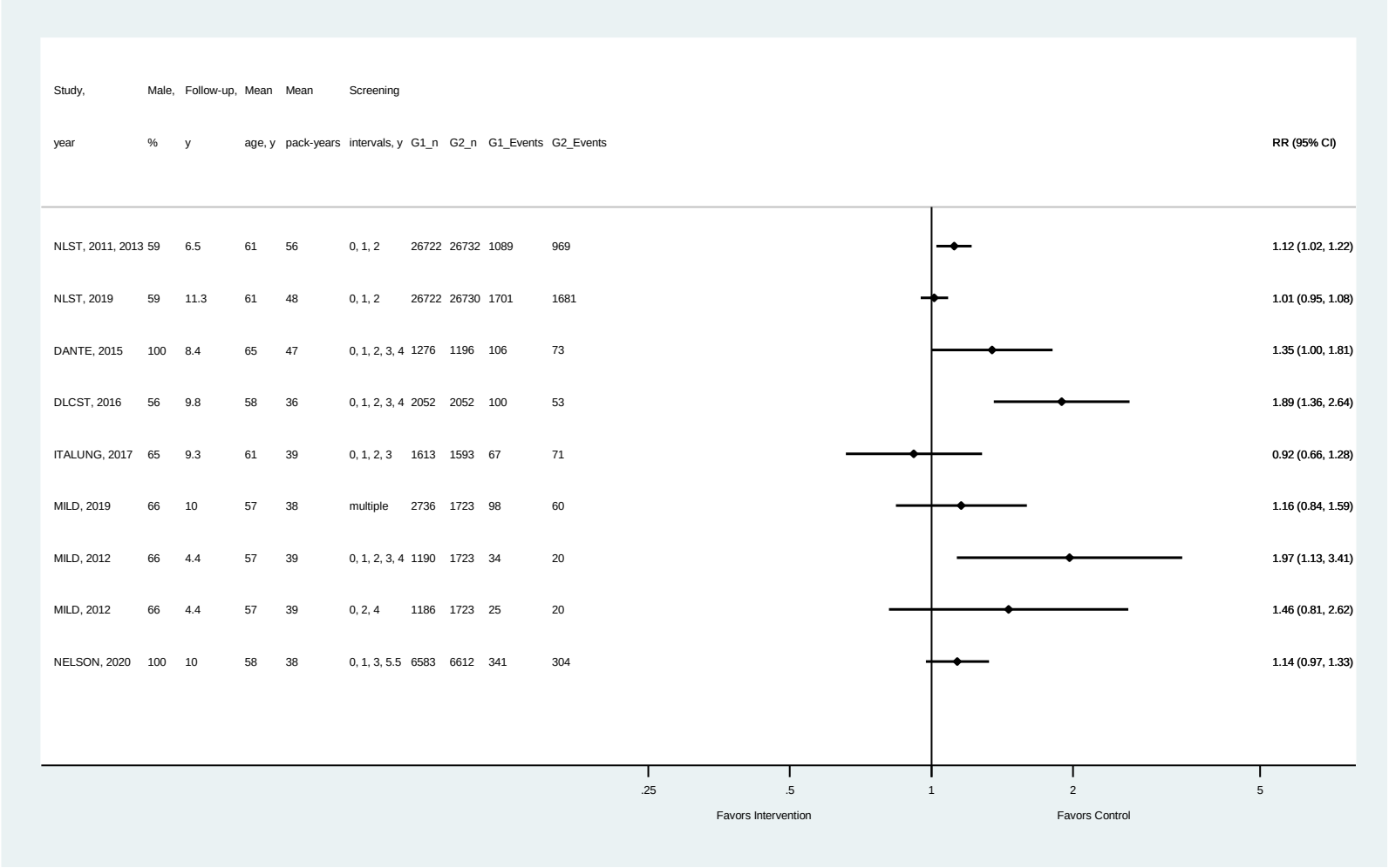
Appendix E Table 9. KQs 6 and 7 Update Search Results: SBRT Study Outcomes

Study Identifiers Author, Year Treatment Type N Enrolled (Analyzed) KQs Addressed Quality	5-Year Survival Outcomes Overall Survival, % (95 CI) Lung Cancer Specific Survival, % (95 CI) Progression- or Recurrence-Free Survival, % (95 CI)	Short-Term Outcomes 30-Day Mortality, N (%) 90-Day Mortality, N (%) Rib Fractures, N (%) Radiation Pneumonitis, N (%) Adverse Event with ≥10% Incidence, N (%)
Westover, 2012[284] SBRT N=15 (20 tumors) KQ 7 Fair	NA	Rib fracture: 3/20 (15*) tumors RP Total: 7/20 (35*) tumors Grade 3: 1/20 (5*) tumor Grade 1: 6/20 (30*) tumors Adverse events Dermatitis: 4/20 (20*) tumors Fatigue: 2/20 (10*) tumors
Wink, 2019[235] SBRT/SABR N=554 KQ 6 Fair	Overall survival: 47	NA
Ye, 2018[294] SBRT/SABR N=100 KQ 7 Fair	NA	30-day mortality: 0 Rib fracture: 0 Acute RP: 6 (6*) Late Grade 2 RP: 8 (8*)

*Indicates that data were calculated by abstractors.

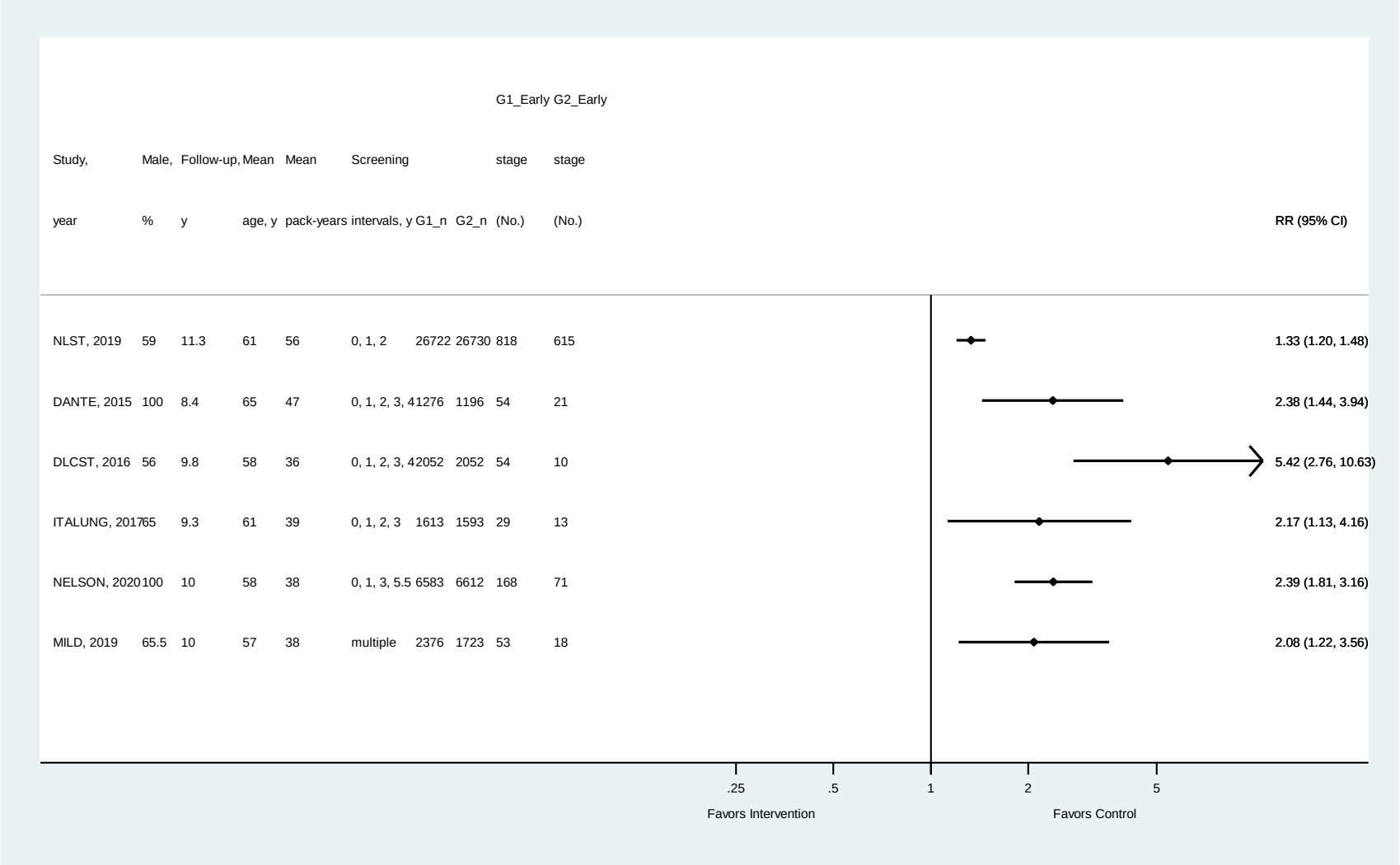
Abbreviations: CI=confidence interval; KQ=key question; Max=maximum; mos=months; NA=not applicable; PSM=propensity score matched; RP=radiation pneumonitis; RR=risk ratio; SABR=stereotactic ablative radiotherapy; SBRT=stereotactic body radiation therapy.

Appendix E Figure 1. Sensitivity Analysis for Trial Results for Lung Cancer Incidence (KQ 1), Including Studies Rated as Poor Quality



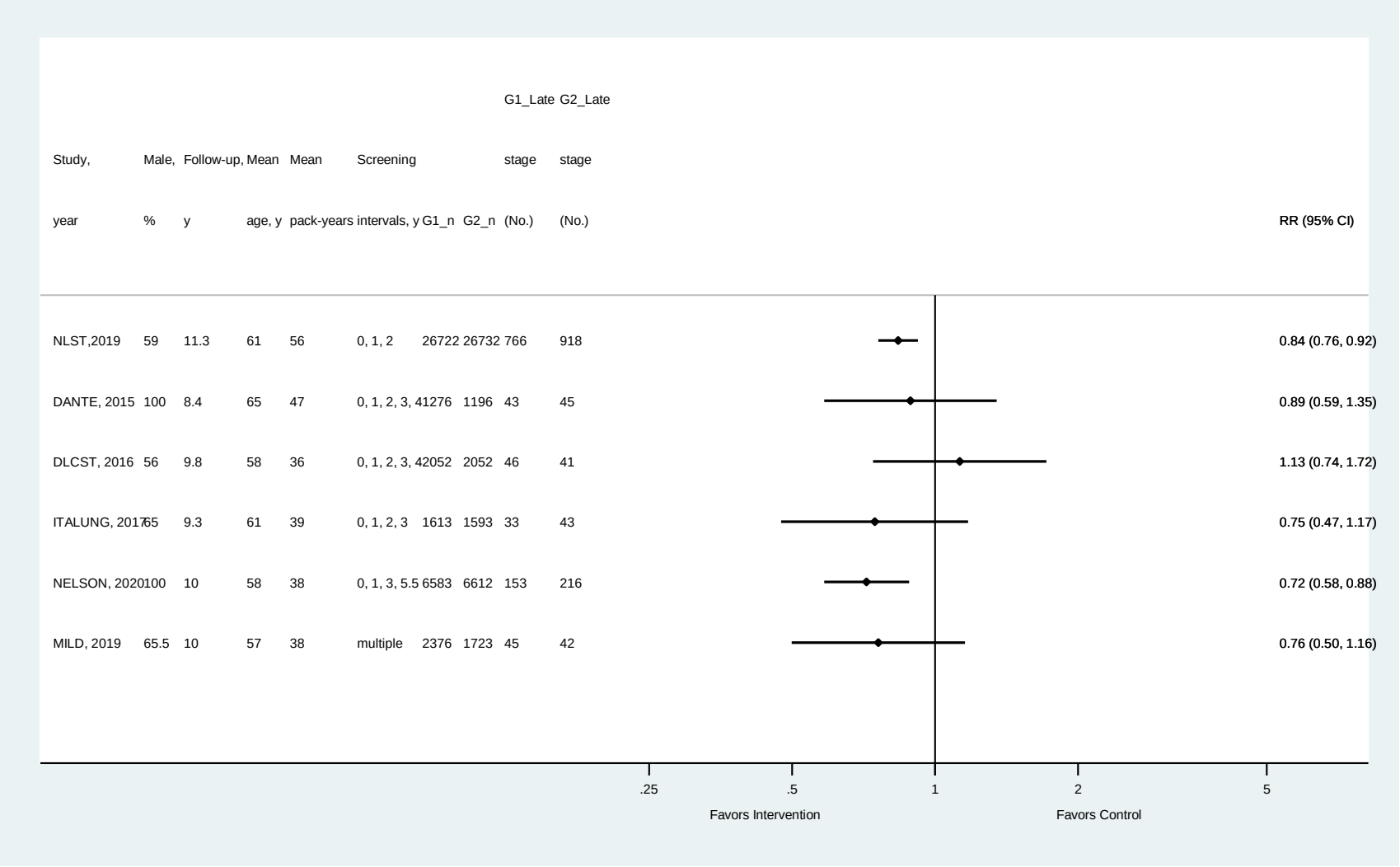
Note: G1=LDCT; G2=Control; The MILD trial randomized participants to annual screening, biennial screening, or a control group. For the 10-year followup, the annual and biennial screening groups were combined. At the 10-year followup, the median duration of screening for those in the screening groups was 6.2 years.
Abbreviations: DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=Italian Lung Cancer Screening Trial; MILD=Multicentric Italian Lung Detection; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial.

Appendix E Figure 2. Sensitivity Analysis for Early-Stage Lung Cancer Incidence (KQ 1), Including Studies Rated as Poor Quality



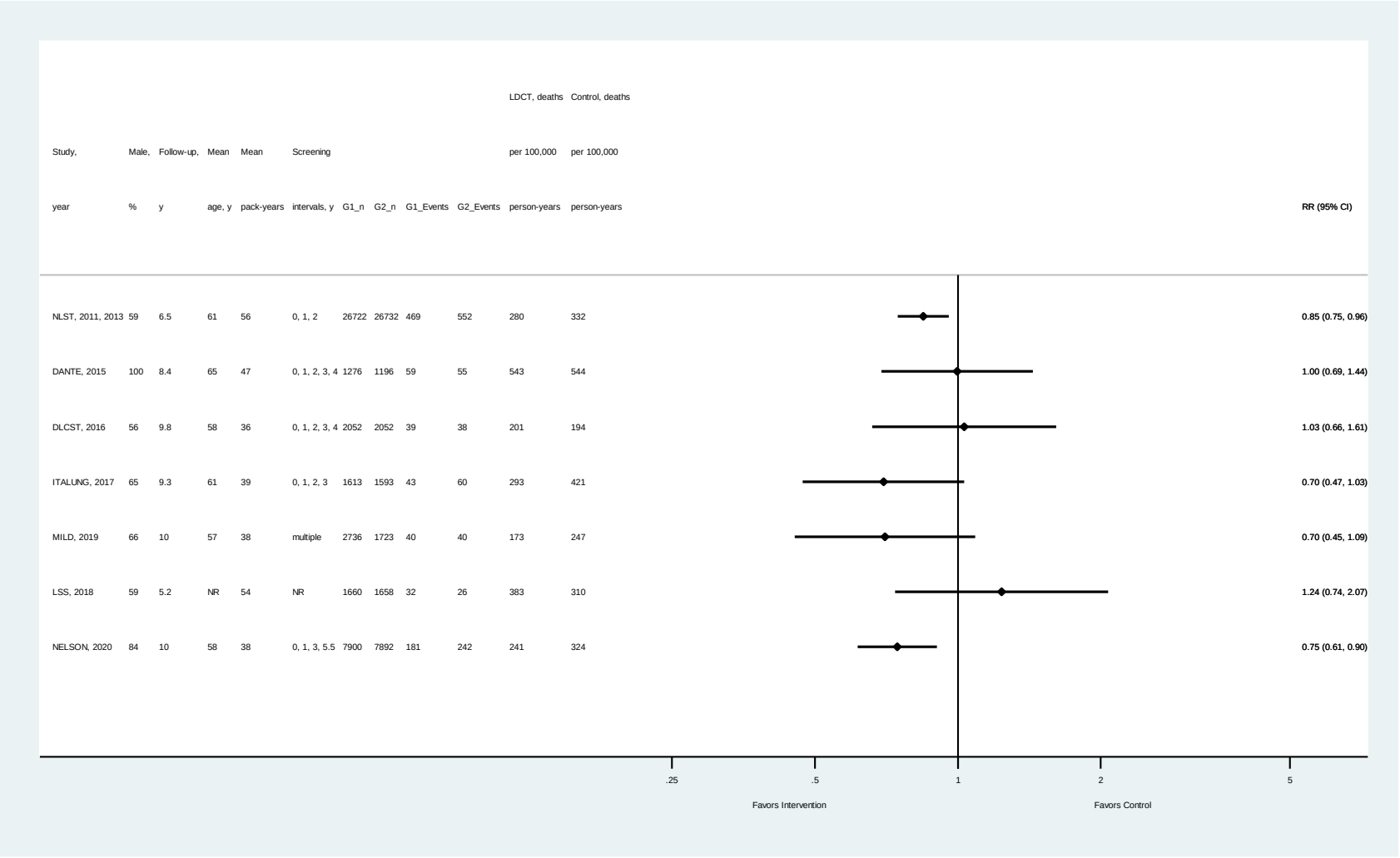
Abbreviations: DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=Italian Lung Cancer Screening Trial; MILD=Multicentric Italian Lung Detection; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial.

Appendix E Figure 3. Sensitivity Analysis for Late-Stage Lung Cancer Incidence (KQ 1), Including Studies Rated as Poor Quality



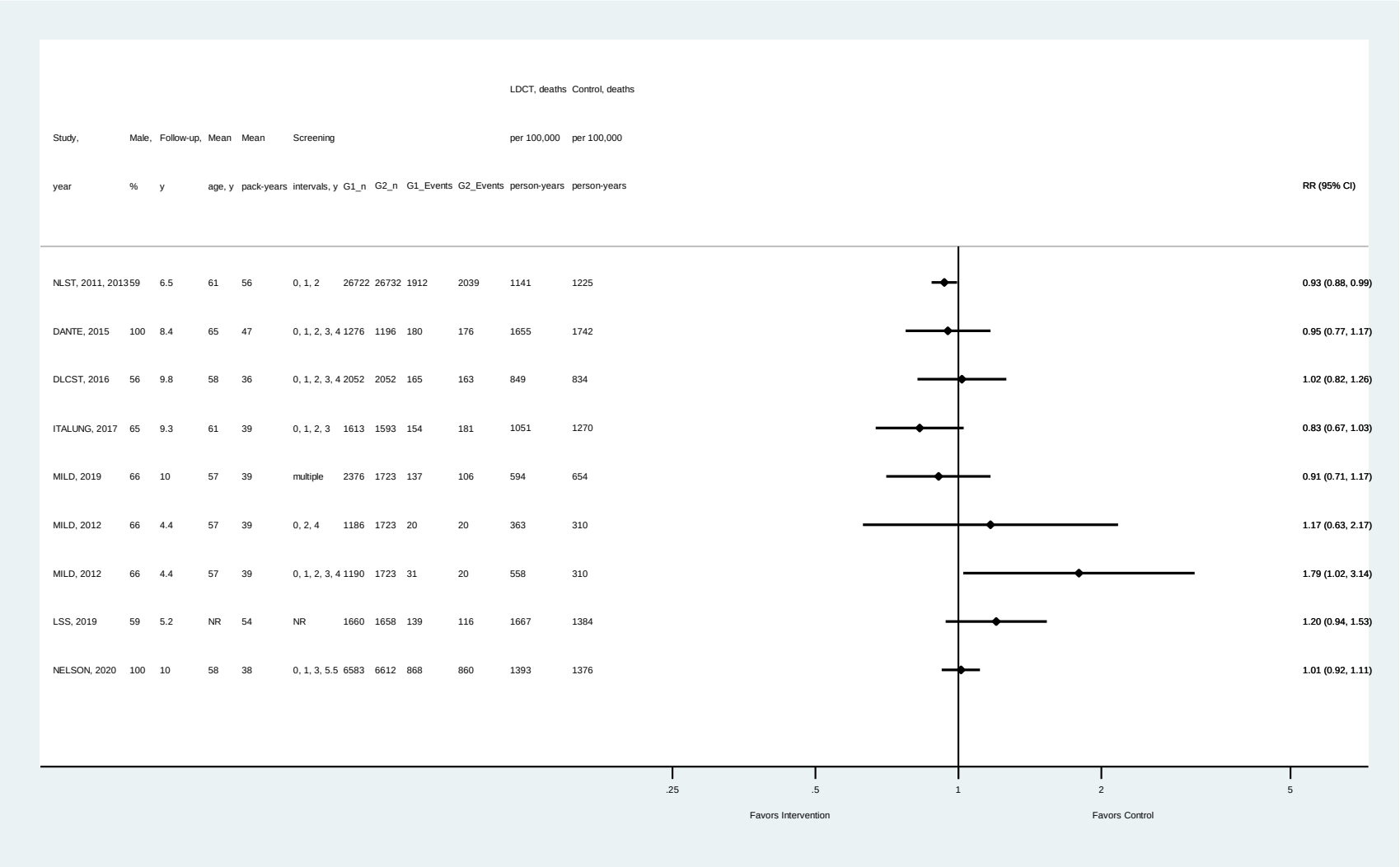
Abbreviations: DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=Italian Lung Cancer Screening Trial; MILD=Multicentric Italian Lung Detection; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial.

Appendix E Figure 4. Sensitivity Analysis for Trial Results for Lung Cancer Mortality (KQ 1), Including Studies Rated as Poor Quality



Abbreviations: DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=Italian Lung Cancer Screening Trial; LSS=Lung Screening Study; MILD=Multicentric Italian Lung Detection; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial.

Appendix E Figure 5. Sensitivity Analysis for Trial Results for All-Cause Mortality (KQ 1), Including Studies Rated as Poor Quality



Abbreviations: DANTE=Detection and Screening of Early Lung Cancer with Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=Italian Lung Cancer Screening Trial; LSS=Lung Screening Study; MILD=Multicentric Italian Lung Detection; NELSON=Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial.