Evidence Synthesis Program

Non-surgical Therapies for Early-stage Non-small Cell Lung Cancer

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from the National Radiation Oncology Program for an evidence review on optimal treatment for stage I lung cancer. The scope was further developed with input from Operational Partners (below), the ESP Coordinating Center, the review team, and the technical expert panel (TEP). The ESP consulted several technical and content experts in designing the research questions and review methodology. In seeking broad expertise and perspectives, divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Ultimately, however, research questions, design, methodologic approaches, and/or conclusions of the review may not necessarily represent the views of individual technical and content experts.

ACKNOWLEDGMENTS

The authors are grateful to the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Technical Expert Panel

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix D for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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ABBREVIATIONS TABLE

Abbreviation	
AHRQ	Agency for Healthcare Research and Quality
AJCC	American Joint Commission on Cancer
ARD	Adjusted risk difference
BAC	Bronchioloalveolar carcinoma
BED	Biologically effective dose
CBO	Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing (Dutch Institute for Healthcare Improvement)
CI	Confidence interval
CT	Computed tomography
CVA	Cerebral vascular accident
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	The 30-item European Organization for Research and Treatment of Cancer Quality of Life Core questionnaire
EQ-5D	The EuroQoL disease-specific questionnaire
ESP	Evidence Synthesis Program
FEV	Fluorodeoxyglucose-positron emission tomography
GDT	Guideline Development Tool
GRADE	Grading of Recommendation, Assessment, Development, and Evaluation
Gy	Gray
HR	Hazard ratio
IASCL	International Association for the Study of Lung Cancer
IQR	Interquartile range
KQ	Key question
L	Left
LC-13	The 13-item lung cancer supplement to the EORTC QLQ-C30
MI	Myocardial infarction
MWA	Microwave ablation
NA	Not available
NCDB	National Cancer Database
NR	Not reported
NSCLC	Non-small cell lung cancer
PET	Positron emission tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
QoL	Quality of life
R	Right
RCT	Randomized controlled trial
RFA	Radiofrequency ablation
RoB	Risk of bias

Abbreviation	
ROSEL	Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer
RR	Risk ratio
SABR	Stereotactic ablative radiotherapy
SBRT	Stereotactic body radiation therapy
SD	Standard deviation
SEER	Surveillance, Epidemiology and End-Results database
STARS	Randomized Study to Compare CyberKnife to Surgical Resection in Stage I Non-Small Cell Lung Cancer
TEP	Technical expert panel
TNM	Tumor, node,metastasis
US/USA	United States of America
USPSTF	US Preventative Services Task Force
VA	Veterans Health Administration
VALOR	Veterans Affairs Lung Cancer Surgery Or Stereotactic Radiotherapy trial
VATB	Video-assisted thoracotomy biopsy
VATL	Video-assisted thoracotomy lobectomy
VATS	Video-assisted thorascopic surgery
VATS L-MLND	Video-assisted thorascopic surgical lobectomy with mediastinal lymph node dissection

EVIDENCE REPORT

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the United States (US), with an estimated 238,340 new cases of lung cancers expected in 2023 and 127,070 estimated deaths.[1] The majority of lung cancers are diagnosed at advanced stages, but with the advent of lung cancer screening, the number of individuals diagnosed with early-stage lung cancer has continued to rise.[2] Within the Veterans Health Administration (VA),[3] approximately 8,000 Veterans are diagnosed with and treated for lung cancer every year. Non-small cell lung cancer (NSCLC) represents approximately 80-85% of lung cancers and includes the following subtypes: adenocarcinoma, squamous cell carcinoma, and large cell lung cancer. With a median age at diagnosis of 70 years, many individuals diagnosed with NSCLC have comorbid conditions due to advanced age and longstanding tobacco use, which may influence the choice of treatment as well as impact patient-important outcomes.

Surgery has been considered the standard of care for individuals with early-stage lung cancer who are deemed medically operable.[4] Surgical treatment includes lobectomy, segmentectomy, wedge resection, and sleeve resection with or without the use of minimally invasive approaches such as robotic or video-assisted thoracoscopic surgery (VATS). Stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) are frequently offered to individuals considered to be medically inoperable for various reasons, including advanced age, inadequate pulmonary reserve, and multiple comorbidities that place them at high risk for severe perioperative complications. Promising results with SBRT/SABR in medically inoperable patients have led to studies evaluating the efficacy and long-term outcomes of SBRT/SABR in medically operable patients, thus raising questions about the optimal treatment approach for early-stage lung cancer.

This review addresses important questions regarding the comparative effectiveness and harms of surgery versus SBRT/SABR, as well as the role of ablative therapies such as radiofrequency ablation, cryoablation, microwave ablation, laser ablation, and brachytherapy in the management of medically operable stage I lung cancer. This is a priority for the VA considering the burden of lung cancer within the VA health care system and the increased number of diagnoses of stage I lung cancer with lung cancer screening. Furthermore, current US Preventive Services Task Force (USPSTF) recommendations for the decision to pursue lung cancer screening are contingent on an individual's ability or willingness to have curative lung surgery.[5] The role of SBRT/SABR in the context of screening decisions or treatment options following a screen-detected or incidentally detected lung cancer is not well outlined but is very relevant to clinical practice and policy decisions. This topic, nominated by the National Radiation Oncology Program, reviews the evidence for the optimal treatment for stage I lung cancer and provides the background rationale for an ongoing VA Cooperative Study, a randomized trial of surgery versus SBRT that is currently enrolling participants.[6] Findings from this review will be used to inform the evidence on the use of treatment modalities in patients with stage I lung cancer who are deemed medically operable.

METHODS

TOPIC DEVELOPMENT

In collaboration with our VA Operational Partners and a technical expert panel (TEP), we developed the key questions and refined the scope of this review. Specifically, while the original protocol focused on surgery compared with non-surgical modalities for patients with stage I lung cancer, the scope of the review was expanded to include an evidence map. The evidence map would outline the body of evidence for comparative studies of ablation therapies in lung cancer, acknowledging the rapidly expanding role for ablation therapy for this indication. Furthermore, comparative effectiveness (and harm) studies for 2 (or more) treatment regimens are best evaluated through randomized head-to-head comparisons, as the body of evidence for comparative effectiveness from observational studies is fraught with issues around confounding (selection bias, performance bias, detection bias) that cannot be fully accounted for using statistical techniques, such as propensity matching. In consultation with our stakeholders and to meet the needs of the National Radiation Oncology Program, the decision was made to include only randomized trials for Key Questions (KQs) 1 and 2. Therefore, this review consists of two parts: 1) a comparative effectiveness review of RCTs comparing surgery to SBRT for stage I non-small cell lung cancer in medically operable patients, and 2) an evidence map of available evidence comparing ablative therapies to other ablative therapies or surgery in either medically operable or inoperable patients.

The term *ablation* can be used to encompass a wide variety of treatment strategies, but in the context of our review, we specifically looked at the following therapies: radiofrequency ablation, cryoablation, microwave ablation, laser ablation, and brachytherapy. Acknowledging that SABR treatment is categorized as an ablative therapy (or implies ablative intent), the published literature suggests that SBRT and SABR are often used interchangeably and without distinction.[7] While SBRT is a broad term used to describe the treatment modality itself, SABR is a better descriptor for the specific treatment that consists of applying highly dose-intensive radiation therapy to limited-volume targets with the effect of achieving local tumor control and even cure.[8] For the purposes of this review, our key questions (and protocol) use the broader term SBRT to encompass both SBRT and SABR, but within the Results and Discussion we use the terms SBRT or SABR as reported by the authors of the primary studies.

The term *medically operable* was not defined *a priori* and we relied on the definition used by the individual studies as their predefined inclusion criteria for enrollment into the study. For the evidence map, we describe the population as reported in the primary studies and included individuals with medically operable as well as medically inoperable lung cancer.

KEY QUESTIONS

The following key questions were the focus of this review:

KQ1: Among adults with medically operable stage I non-small cell lung cancer, what are the benefits and harms of SBRT compared to surgery?

KQ2: Do benefits and harms of SBRT/SABR compared to surgery differ by patient characteristics (*eg*, age, comorbidities, performance status), tumor characteristics (size, location, stage), surgery characteristics (type of surgery [minimally invasive vs open],

type of resection [lobectomy, wedge resection, segmental resection, sleeve resection]), or SBRT characteristics (*eg*, dose, fractionation)?

KQ3: What are the quantity and characteristics of evidence assessing the comparative effects of ablative therapies as monotherapy or combined with other ablative therapies versus surgical, radiotherapy, or ablative therapies for patients with early stage I non-small cell lung cancer, by type of intervention, patient/tumor characteristics, study design, and outcomes?

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42022377940).

DATA SOURCES AND SEARCHES

Two search strategies were developed, one to address KQs 1 and 2, and a second for KQ3. We searched MEDLINE and Embase from inception to September 2022. We supplemented these searches with a review of relevant systematic review bibliographies. Relevant systematic reviews were identified by keyword searches of the AHRQ, Cochrane, and VA ESP databases, suggestions by content experts, or reviews found and noted during abstract triage. We limited the searches to published and indexed articles involving human subjects available in the English language (see Appendix A for complete search strategies).

STUDY SELECTION

After duplicates were removed, citations were uploaded into DistillerSR.[9] Using prespecified inclusion/exclusion criteria as described below in Table 1 for each KQ, titles and abstracts were screened independently by at least 1 reviewer for potential relevance. Any article excluded at the abstract level required confirmation by a second reviewer; articles included by either reviewer were advanced to the full-text review stage. At the full-text screening stage, 2 independent reviewers agreed on the final inclusion and exclusion decision. Disagreements were resolved by consensus among the review team. Articles that met eligibility criteria were included for data abstraction. A PRISMA flowchart documents the process of study selection and the total number of identified, included, and excluded studies. A complete list of citations excluded at full-text review can be found in Appendix B.

Table 1. Eligibilty Criteria

	Key Questions 1 and 2	Key Question 3
Population	Adults, 18 years or older, with medically operable stage I non-small cell lung cancer	Adults, 18 years or older, with medically operable or inoperable stage I non-small cell lung cancer
Intervention	Stereotactic body radiation therapy (SBRT)/stereoablative radiation therapy (SABR)	Non-surgical ablative treatment modalities: • Cryoablation • Radiofrequency ablation • Microwave ablation • Laser ablation • Brachytherapy

	Key Questions 1 and 2	Key Question 3
Comparator	Surgery, including wedge resection, segmental resection, lobectomy (including sleeve resection)	• Surgery, including wedge resection, segmental resection, lobectomy (including sleeve resection) • Ablative therapies: cryoablation, radiofrequency ablation, microwave ablation, laser ablation, brachytherapy • Radiotherapy (SBRT/SABR and conventional)
Outcomes	• Overall survival • Lung-cancer-specific survival • Local/regional recurrence/control • Systemic/distant recurrence/control • Overall/global quality of life • SBRT toxicity (grade 2-5 cough, pneumonitis, esophagitis) • Hospital readmissions • Short-term (<30 days) respiratory complications (pneumonia, hemothorax, pneumothorax, air leak, oxygen dependence at discharge) • Short-term (<30 days) cardiovascular complications (pneumonia, hemothorax, pneumothorax, air leak, oxygen dependence at discharge) • Long-term (>30 days) respiratory complications (cough, pneumonia, dyspnea, oxygen dependence) • Long-term (>30 days) pain (requiring medical intervention)	• Overall survival • Lung-cancer-specific survival • Local/regional recurrence/control • Systemic/distant recurrence/control • Overall/global quality of life • Lung cancer specific quality of life validated scale item • SBRT toxicity (grade 2-5 cough, pneumonitis, esophagitis) • Hospital readmissions • Short-term (<30 days) respiratory complications (cough, pneumonia, hemothorax, pneumothorax, air leak, oxygen dependence at discharge) • Short-term (<30 days) cardiovascular complications (pneumonia, hemothorax, pneumothorax, air leak, oxygen dependence at discharge) • Post-ablative syndrome • Long-term (>30 days) respiratory complications (cough, pneumonitis, pneumonia, dyspnea, oxygen dependence)
Timing	Any	Any
Setting	Clinical	Clinical
Study Design	RCTs	RCTs and observational studies with a comparative arm

Abbreviations. RCT=randomized controlled trial.

DATA ABSTRACTION AND ASSESSMENT

Data from eligible studies were abstracted into customized DistillerSR databases by 1 reviewer and verified by a second reviewer. Any disagreements were resolved by consensus between the 2 reviewers or arbitrated by the study team.

For KQs 1 and 2, we abstracted the following information: trial characteristics (*eg,* inclusion/exclusion criteria), sample size, intervention and comparison characteristics, demographic information (*eg,* age, tumor stage), surgery characteristics, SBRT characteristics, and any information related to outcomes of interest. In addition to data from published articles, trial investigators were contacted and asked to provide data stratified by treatment arm (if available) to supplement the published data.

Two reviewers independently assessed risk of bias (RoB) using the Cochrane RoB 2 tool and resolved disagreements via discussion and consensus amongst the review team.[10] For each study, we assessed the risk of bias for each domain as being low, high, or unclear. Ratings for all eligible studies for KQs 1 and 2 can be found in Appendix C.

For KQ3, we abstracted the following information: sample size, interventions and comparisons, demographic information (*eg,* age), country, study design, surgery and ablation therapy characteristics, and outcomes reported. As KQ3 consisted of an evidence map, no formal risk of bias assessment was performed for studies meeting eligibility criteria.

SYNTHESIS

For KQs 1 and 2, we identified a publication that conducted a quantitative analysis of data from the 2 trials and used this to inform our review. We evaluated the overall certainty of evidence for each outcome according to the GRADE approach, which considers 5 criteria (risk of bias, inconsistency, imprecision, publication bias, and indirectness). One author independently rated the certainty of evidence for each outcome as high, moderate, low, or very low using GRADEpro GDT.[11,12] Any disagreement was resolved through group consensus. We evaluated the certainty of evidence for the following outcomes: overall survival, lung-cancer-specific survival, quality of life, and adverse events of grade 2 or higher. The summary of the evidence for the main outcomes is presented in a summary of findings table (Table 4), which provides key information regarding the best estimate of the magnitude of the effect in relative and absolute differences for each comparison of alternative management strategy, number of participants and studies, addressing each outcome, and a rating of the overall confidence in the estimates for each outcome.

For KQ3, we relied on data visualization techniques to summarize the data for the evidence map. No formal synthesis of study results was performed and no assessment of the quality of individuals studies was conducted. We summarized the data narratively and provided visual graphics including tables and a bubble plot to summarize the key features of the studies. We mapped the results by types of studies, types of interventions versus comparisons, and types of outcomes. We used Microsoft Excel to create the figures and tables. We sought and iteratively incorporated feedback on visualization and usability from our review team.

RESULTS

KEY QUESTIONS 1 AND 2

KQ1: Among adults with medically operable stage I non-small cell lung cancer, what are the benefits and harms of stereotactic beam radiotherapy (SBRT) compared to surgery?

KQ2: Do benefits and harms of SBRT/SABR compared to surgery differ by patient characteristics (*eg*, age, comorbidities, performance status), tumor characteristics (size, location, stage), surgery characteristics (type of surgery [minimally invasive vs open], type of resection [lobectomy, wedge resection, segmental resection, sleeve resection]), or SBRT characteristics (*eg*, dose, fractionation)?

Literature Flow

The literature flow diagram (Figure 1) summarizes the results of the study selection process. The full list of excluded studies is available in Appendix B.

Literature Overview

Our search identified 2,959 potentially relevant citations. After title and abstract screening, 27 were moved forward to full-text review. Of those 27, we identified only 2 publications which met inclusion criteria for KQ1. Studies were excluded for the following reasons: ineligible publication type or study design (*eg,* commentaries or non-randomized studies), ineligible intervention or outcome (*eg,* radiotherapy vs chemotherapy or chemoradiation), and ineligible outcome (*eg,* treatment preferences). No eligible publications were identified that addressed KQ2.

One publication, Chang et al,[13] pooled data from 2 randomized trials: the Randomized Study to Compare CyberKnife to Surgical Resection In Stage I Non-Small Cell Lung Cancer (STARS) trial and the Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer (ROSEL) trial. Both trials had similar inclusion criteria (Table 2) and both were terminated early due to low recruitment. Both trials reported overall survival at 1 and 3 years, 3-year recurrence-free survival, and adverse events. The clinical trials had similar enrollment criteria with minor differences: histological confirmation was not required for the ROSEL trial as compared to the STARS trial, and follow-up intervals in the STARS trial were longer. Table 3 describes the STARS and ROSEL trial population characteristics and results individually, as well as the pooled results as reported in the Chang et al[13] article. Data from the STARS trial were obtained from Clinicaltrials.gov, and data from the ROSEL trial were provided by trial investigators. The second publication, Louie et al,[14] reported quality of life data from the ROSEL trial. Both publications were judged to have “some concerns” for risk of bias.

Figure 1. KQs 1 and 2 Literature Flowchart

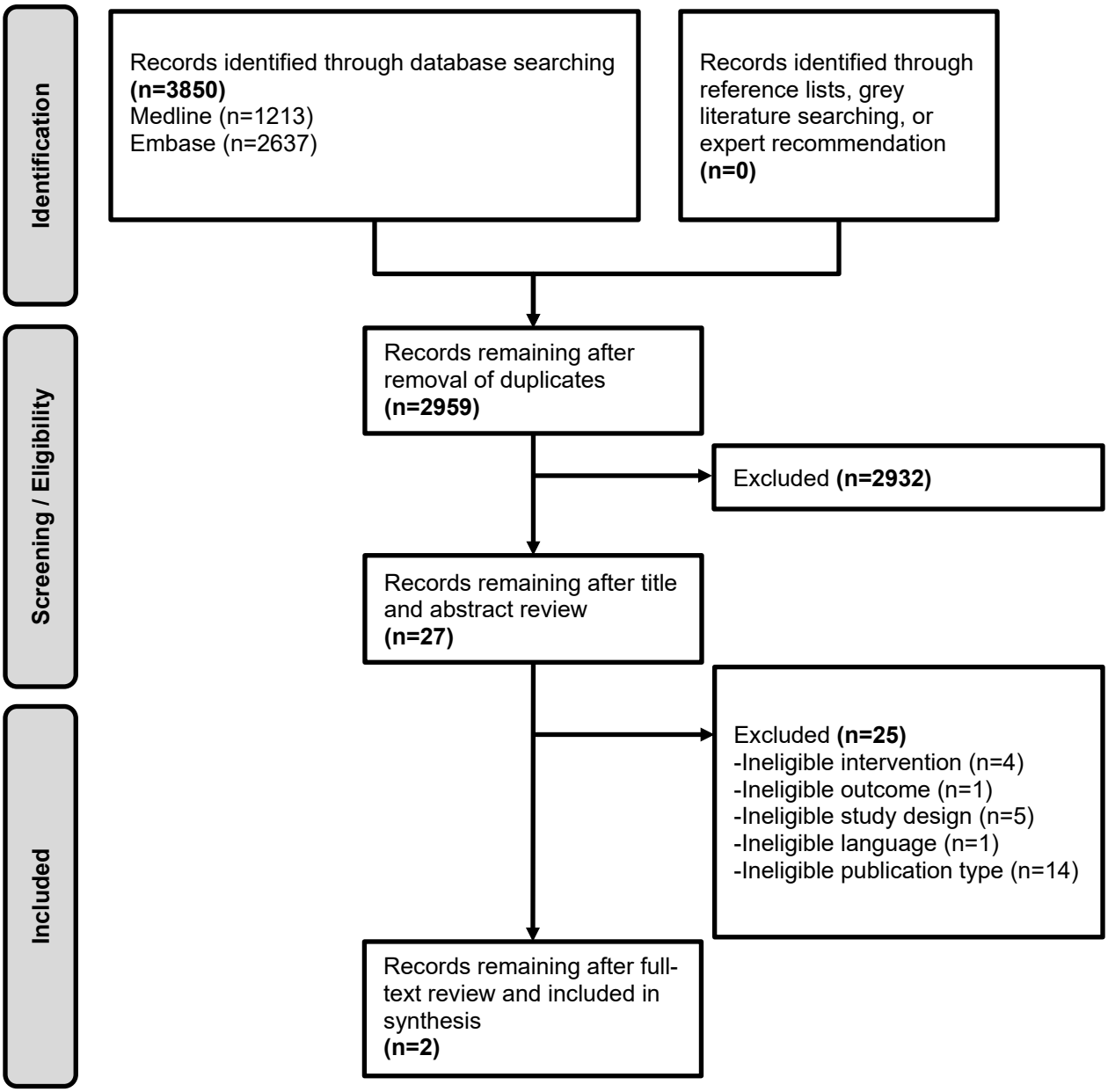

Table 2. Overview of STARS (Randomized Study to Compare CyberKnife to Surgical Resection in Stage I Non-small Cell Lung Cancer) and ROSEL (Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer) Clincial Trial Information

Characteristics	STARS	ROSEL
Trial #	NCT00840749	NCT00687986
Country	28 sites in USA, China, and France (7 sites enrolled participants)	10 sites in Netherlands (4 sites enrolled participants)
Funding	Accuray (Industry)	Netherlands Organization for Health Research and Development
Inclusion criteria	• Patients with a histological confirmation of non-small cell cancer required by either biopsy or cytology. The following primary cancer types were eligible: squamous cell carcinoma, adenocarcinoma with or without BAC features, large cell carcinoma with or without neuroendocrine features, neuroendocrine carcinoma, bronchioloalveolar cell carcinoma, or non-small cell carcinoma not otherwise specified. • Patients had to have appropriate staging studies identifying them as specific subsets of the revised IASCL state IA or IB based on only 1 of the following combinations of TNM staging: T1, N0, M0 or T2 (≤4 cm), N0, M0. • Mandatory staging studies were done within 8 weeks prior to study entry. A PET/CT scan was required. • Patients with hilar or mediastinal lymph nodes with short axis diameter <1 cm and no abnormal hilar or mediastinal uptake on PET were considered N0. Patients with >1 cm short axis diameter of hilar or mediastinal lymph nodes on CT or abnormal PET (including suspicious but non-diagnostic uptake) were still eligible if directed tissue biopsy of all abnormally identified areas were negative for cancer. Solitary pulmonary lesions <4 mm were not considered significant. • Patients had to be considered reasonable candidates for surgical resection of the primary tumor. Standard justification for deeming a patient medically operable based on pulmonary function for surgical resection of NSCLC included any of the following: baseline FEV1 >40%	• Patients with a cytological or histological diagnosis of stage IA non-cell lung cancer diagnosed in accordance with Dutch CBO guidelines. When no pathological diagnosis was available, a patient with a new or growing pulmonary lesion with radiological features consistent with malignancy AND a lesion showing uptake on a FDG-PET scan were eligible. • No evidence of regional or distant metastases on a standardized FDG-PET scan within 6 weeks of any protocol treatment • The medial extension of tumors at least 2 cm away from main and lobar bronchi, and also minimum of 1.5 cm from large peripheral blood vessels such as the aorta and main pulmonary artery. Lesions of at least 2 cm from the mediastinal pleura eligible if the responsible radiation oncologist judged that the specified normal tissue tolerance doses specified in the protocol were not to be exceeded. • Patients who were judged by a multi-disciplinary team to have 2 primary lung tumors (on the basis of clinical, radiological, FDG-PET and/or cyto-pathology findings) were eligible for randomization provided that both surgery and SRT could be performed in accordance with protocol requirements. • Patient had to be fit to undergo a complete surgical resection of the lesion in accordance with 2004 Dutch CBO guidelines. • Performance score of ECOG ≤2 was required before any treatment.

Characteristics	STARS	ROSEL
	predicted, post-operative predicted FEV1 >30% diffusion capacity >40% predicted, absent baseline hypoxemia and/or hypercapnia, exercise oxygen consumption >50% predicted, absent severe pulmonary hypertension, absent severe cerebral, cardiac, or peripheral vascular disease, and absent severe chronic heart disease. • Patients had to be ≥18 years of age • Patient's Zubrod performance status had to be Zubrod 0-2	
Exclusion criteria	• Patients with primary tumors >4 cm • Patients with well-differentiated neuroendocrine carcinoma (carcinoid tumor) • Patients in whom acceptable SRT planning to meet minimal requirement of target coverage and dose-volume constraints of critical structures were not achievable • Evidence of regional or distant metastases, or synchronous primary or prior malignancy in the past 5 years other than non-melanomatous skin cancer or in situ cancer • Prior lung or mediastinal radiotherapy • Plans for concomitant local therapy (including standard fractionated radiotherapy and surgery) while on this protocol except at disease progression • Pregnant or lactating women (as treatment involved unforeseeable risks to the embryo or fetus)	• Patients with any unstable systemic disease (including active infection, uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction within the previous year, severe cardiac arrhythmia requiring medication, hepatic, renal or metabolic disease). • Prior or active malignancy (other than NSCLC) unless treated more than 3 years prior with curative intent and no recurrence, with the exception of non-melanoma skin cancers or in-situ cervical cancers • Prior chemotherapy or radiotherapy for the present diagnosis of NSCLC • Plans for concomitant treatment with any other experimental drug under investigation • Pregnancy • Men and women of child-bearing potential who were not using effective means of contraception for 6 months after treatment
Radiotherapy characteristics	CyberKnife system (Accuray, Sunnyvale, CA, USA) was used for all radiotherapy sessions. Patients with peripherally located lesions (*ie*, those located >2 cm in any direction from the proximal bronchial tree, major vessels, oesophagus, heart, tracheal, vertebral body, pericardium, mediastinal pleural, and brachial plexus) received a total radiation dose of 54 Gy in three 18 Gy fractions (BED 151.2 Gy), calculated with a Monte Carlo or equivalent algorithms or its equivalent dose if other algorithms were used and heterogeneity correction. For central lesions (*ie*, those within 2 cm of these structures), 50 Gy in 4 12.5 Gy fractions (BED 112.5 Gy) was used. The	Linear-accelerator-based SABR from multiple vendors was used. Only lesions located 2 cm or more from the hilar structures on the diagnostic CT scan were eligible. A toxicity risk-adapted fractional scheme was used in which a total dose of 54 Gy in 3 18 Gy fractions (BED 151.3 Gy), calculated with a Monte Carlo or equivalent algorithms or its equivalent doses if other algorithms were used and heterogeneity correction, and given over 5–8 days; alternatively, a total dose of 60 Gy at 5 12 Gy fractions (BED 132.0 Gy), was given over 10–14 days (to account for different treatment-delivery practices in Dutch centers). The SABR dose prescription was chosen

Characteristics	STARS	ROSEL
	SABR dose was prescribed to the highest isodose line, which was required to cover 100% of the gross tumor volume (defined as visible disease in CT images with use of lung window) and more than 95% of the planning target volume (defined as the gross tumor volume plus a 3 mm margin). Coverage of 100% of the planning target volume by at least the prescription dose was encouraged. The normal tissue constraints were met for all cases. Treatment delivery was recommended to be complete within 5 days of its initiation.	such that 95% of the planning target volume, the internal target volume (based on four-dimensional CT), or other equivalent approaches to take tumor motion into consideration—plus a 3–5 mm margin for setup and motion uncertainty—would receive at least the nominal fraction dose, and 99% of the planning target volume would receive at least 90% of the fraction dose. The preferred maximum dose within the planning target volume was between 110% and 140% of the prescribed dose.
Surgery characteristics	Both open thoracotomy and video-assisted thoracotomy (VATS) were acceptable procedures. Surgery could consist of a lobectomy, sleeve resection, bi-lobectomy, or pneumonectomy as determined by the attending surgeon based on the operative findings.	Any anatomical surgical resection with lymph node dissection

Abbreviations. BAC=bronchoalveolar carcinoma; BED=biologically effective dose; CBO=Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing (Dutch Institute for Healthcare Improvement); CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; FEV=forced expiratory volume; FDG-PET=fluorodeoxyglucose-positron emission tomography; IASCL=International Association for the Study of Lung Cancer; SABR=stereotactic ablative radiotherapy; TNM=tumor, node, metastasis; USA =United States of America.

Overall Survival at 3 Years

Overall survival at 3 years, using pooled data from the STARS and ROSEL trials on 58 patients, was reported in 1 publication.[13] When compared to surgery, the HR for 3-year overall survival was 0.14 (95% CI [0.017, 1.19]) based on follow-up of 35-40 months. However, both the radiotherapy and surgery arm had a very small number of deaths at 3 years, 1 in the SABR/SBRT arm and 5 in the surgery arm. Based on the limited number of individuals who underwent non-invasive surgery and based on both trials being terminated early, we are very uncertain about the effect of SABR/SBRT on overall survival at 3 years, as compared with surgery (very low certainty of evidence). A summary of findings is presented in Table 4.

Recurrence-Free Survival

Recurrence-free survival at 3 years was reported in the same publication[13] using pooled data from the STARS and ROSEL trials. When compared to surgery, over a follow up of 35-40 months, the HR was 0.69 (95% CI [0.21, 2.29]). However, as outlined above, the effect of SABR/SBRT on recurrence-free survival at 3 years compared to surgery is very uncertain (very low certainty of evidence).

Adverse Events

The same publication reported on grade ≥3 adverse events, using pooled data on 58 patients from the STARS and ROSEL trials.[13] When compared to surgery, the effect of SABR on grade ≥3 adverse events is very uncertain (Table 4). Specific adverse events as captured and reported by the individual trials are summarized in Table 3. Three grade ≥3 adverse events were reported across the 2 arms in the STARS cohort ($N = 36$). Sixteen grade ≥3 adverse events were reported across the 2 arms of the ROSEL cohort: 7 events in the SABR/SBRT arm ($N = 11$) and 9 events in the surgery arm ($N = 11$).

Quality of Life

One publication addressed quality of life (QoL) in participants ($N = 19$) treated with SABR compared to surgery, using data from the ROSEL trial.[14] In this study, the following tools (administered at baseline, 3, 6, 12, 18, and 24 months) were used to assess QoL: the 30-item European Organization for Research and Treatment of Cancer Quality of Life Core questionnaire (EORTC QLQ-C30, 13-item lung cancer supplement [LC-13] and the EuroQoL disease-specific questionnaire [EQ-5D]). Minimum thresholds of a 10-point decrease (for global and functional scales) and increase (for symptom scales and items) were used to denote a clinically meaningful difference. The following scales/items were reported: physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, global health status/QoL, fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial problems, coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts, and dyspnea. If at any point in the study period the participant had a ≥10-point decrease from a prior rating, this was considered a meaningful event. In all comparisons, only global health status was found to be significantly worse on univariable Cox proportional hazard modeling for surgical patients when compared to SABR (HR = 0.19; 95% CI [0.04, 0.91]). However, this is based on a small number of patients with limited number of events and low rates of minimally invasive surgery (Table 5). Therefore, when compared to surgery, the effect of SABR on quality of life is very uncertain (very low certainty of evidence).

Table 3. Study Characteristics for All Eligible Trials Reporting Survival or Adverse Events

Characteristics & Outcomes	STARS*		ROSEL†		Chang (Pooled STARS & ROSEL)	
	SABR	Surgery	SABR	Surgery	SABR	Surgery
Baseline Characteristics						
N (% female)	36 (50)		11 (27)	11 (36)	31 (55)	27 (59)
Age	18-65: 16 (44) ≥65: 20 (56)		Median (IQR): 65 (61-71)	Median (IQR): 65 (62-72)	Mean (SD): 67.3 (9.2)	Mean (SD): 67.3 (8.2)
Median follow-up (IQR)	NR		Median (IQR): 42 months (20-54)		40.2 months (23.0 to 47.3)	35.4 months (18.9 to 40.7)
Tumor location N (%):	NR		Lower L: 5 (45) Upper L: 1 (9) Lower R: 2 (18) Middle R: 1 (9) Upper R: 2 (18)	Lower L: 2 (18) Upper L: 4 (36) Lower R: 0 (0) Middle R: 0 (0) Upper R: 5 (45)	Lower L: 7 (23) Upper L: 7 (23) Lower R: 5 (16) Middle R: 3 (10) Upper R: 9 (29)	Lower L: 4 (15) Upper L: 8 (30) Lower R: 1 (4) Middle R: 2 (7) Upper R: 12 (44)
Tumor stage: N (%)	NR‡		NA = 11‖	T0: 1 (9) T1: 9 (82) T2: 1 (9)	T1a: 16 (52) T1b: 11 (35) T2a: 4 (13)	T1a: 18 (67) T1b: 8 (30) T2a: 1 (4)
Type of radiotherapy or surgery	54 Gy/3 Fx: 16 50 Gy/4 Fx: 4	NR	54 Gy in 3 18 Gy fractions over 5-8 days: 6 60 Gy at 5 12 Gy fractions over 10-14 days: 5	Lobectomy: 10 Wedge resection: 1	--	Open lobectomy: 19 VATL: 5 VATB: 1 Wedge resection: 1 Aborted resection: 1
Survival Outcomes						
3-year overall survival (n/N)	31/36		10/11	10/11	95% (85 to 100) 30/31	79% (64 to 97) 22/27
					HR = 0.14 (0.017 to 1.190), $p = 0.037$	
3-year recurrence-free survival (n/N)	NR		9/11	8/11	86% (74 to 100) 26/31	80% (65–97) 21/27
					HR = 0.69 (0.21 to 2.290), $p = 0.54$	

Characteristics & Outcomes		STARS*		ROSEL†		Chang (Pooled STARS & ROSEL)	
		SABR	Surgery	SABR	Surgery	SABR	Surgery
Adverse Events							
Any treatment-related grade 2+ adverse events (n/N)		3/36		7/11	9/11	Grade 3+: 9.7% (-24 to 43)‡ 3/31	Grade 3+: 48% (21 to 75)‡ 13/27
Grade 2+ dyspnoea or cough (n/N)		0/36		5/11	6/11	Grade 3+: 6% (2/31)	Grade 3+: 19% (5/27)
SBRT toxicity	Grade 2+ pneumonitis (n/N)	0/36		0/11	0/11	NR	
	Grade 2+ esophagitis	NR		NR		NR	
Short-term (≤30 days)	Respiratory complications (pneumonia, hemothorax, pneumothorax, air leak, oxygen dependence at discharge)	NR		NR		NR	
	Cardiovascular complications (MI/CVA/atrial fibrillation)	0/36		2/11	0/11	NR	
	Hospital readmissions	NR		NR		NR	
Long-term (>30 days)	Respiratory complications (cough, pneumonia, dyspnea, oxygen dependence)	NR		NR		NR	
	Pain (requiring medical intervention)	NR		NR		NR	

Notes. *Data taken from results posted on clinicaltrials.gov; trial investigators were contacted.
† Data was provided by principal investigator of ROSEL trial.
‡ Calculated by review authors.
ǂ Authors used International Association for the Staging of Lung Cancer (IASLC) 8th edition to stage participants.
ǀ Authors used American Joint Commission on Cancer (AJCC) 7th edition to stage participants.
Abbreviations. CVA=cerebral vascular accident; Gy=Gray; HR=hazard ratio; IQR=interquartile range; L=left; MI=myocardial infarction; NA=not available; NR=not reported; R=right; ROSEL=Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer; SABR=stereotactic ablative radiotherapy; SD=standard deviation; STARS=Randomized Study to Compare CyberKnife to Surgical Resection in Stage I Non-small Cell Lung Cancer; VATB=video-assisted thoracotomy biopsy; VATL=video-assisted thoracotomy lobectomies.

Table 4. Certainty of Evidence for SABR/SBRT versus Surgery for Lung Cancer Outcomes

Outcome	Median Follow-up No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)		Certainty	What Happens
			Risk with Surgery	Risk Difference with SBRT/SABR		
3-year overall survival	35-40 months *N* = 58 (2 RCTs)	**HR = 0.14** (0.017, 1.19)	815 per 1,000	157 more survived per 1,000 (31 fewer to 182 more)	⊕◯◯◯ Very Low[a,b,c]	The evidence is very uncertain about the effect of SABR/SBRT on overall survival.
3-year recurrence-free survival	35-40 months *N* = 58 (2 RCTs)	**HR = 0.69** (0.21, 2.29)	778 per 1,000	63 more survived per 1,000 (215 fewer to 171 more)	⊕◯◯◯ Very Low[a,b,c]	The evidence is very uncertain about the effect of SABR/SBRT on recurrence-free survival.
Grade ≥3 adverse events	35-40 months *N* = 58 (2 RCTs)	**RR = 0.27**† (0.08, 0.87)	481 per 1,000	351 fewer had a Grade ≥3 adverse event per 1,000 (443 fewer to 63 fewer)	⊕◯◯◯ Very Low[a,b,c]	The evidence is very uncertain about the effect of SABR/SBRT on grade ≥3 adverse events.
Reduction in quality of life	42 months *N* = 22 (1 RCT)	**RR = 0.41**† (0.11, 1.59)	800 per 1,000	472 fewer had a reduction in quality of life per 1,000 (712 fewer to 472 more)	⊕◯◯◯ Very Low[a,b,c]	The evidence is very uncertain about the effect of SABR/SBRT on quality of life.

Notes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
† Calculated by review authors.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded for study limitations (lack of blinding of participants, investigators, and outcome adjudicators). Both studies terminated early due to issues with enrollment.
b. Downgraded 2 levels for imprecision due to very small number of events.
c. Downgraded for indirectness. The surgery group had low rates of minimally invasive surgical resection (*eg,* VATS).

Table 5. Study Characteristics for All Eligible Publications Reporting Quality of Life

Author, Year Risk of Bias Trial(s)	Characteristics & Outcomes	Surgery	SABR	Results
Louie, 2015[14] Some concerns ROSEL	N (% female)	11 (27)	11 (36)	-
	Median age (range)	65 (59-74)	65 (52-75)	-
	Median follow-up (range)	42 months (6-61)		-
	Tumor stage: N (%)	T0: 1 (9) T1: 9 (82) T2:1 (9)	Not available	-
	*Reduction in quality of life	8/10	2/9	HR = 0.19 *p* = 0.038

Notes. *Quality of life data were not reported from 3 participants.
Abbreviations. HR=hazard ratio; ROSEL=Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer; SABR=stereotactic ablative radiotherapy.

KEY QUESTION 3

KQ3: What are the quantity and characteristics of evidence assessing the comparative effects of ablative therapies as monotherapy or combined with other ablative therapies versus surgical, radiotherapy or ablative therapies for patients with early stage I non-small cell lung cancer, by type of intervention, patient/tumor characteristics, study design, and outcomes?

Literature Flow

The literature flow diagram (Figure 2) summarizes the results of the study selection process. The full list of excluded studies is available in Appendix B.

Literature Overview

Of 3,095 potentially relevant citations after title and abstract screening, 131 were moved forward to full-text review. Of those 131, we identified 18 publications which met inclusion criteria for KQ3.

Data Visualization

Study Characteristics and Patient Population (Map 1)

No RCTs of ablation therapy were identified from our review; all the included studies were observational studies with a comparator group. Most publications were observational single-site retrospective cohort studies ($k = 10$),[15-24] while fewer used multisite retrospective data ($k = 2$).[25,26]

The majority of the publications on ablative therapies were conducted in the US ($k = 9$)[15,17,24,27-32]; other countries included China ($k = 3$),[18,23,26] Japan ($k = 2$),[19,25] Italy ($k = 2$),[16,21] South Korea ($k = 1$)[20] and Germany ($k = 1$).[22] Six publications used national US databases, including the National Cancer Database (NCDB) ($k = 4$)[27,28,30,32] and the Surveillance, Epidemiology and End-Results Database (SEER) ($k = 2$).[29,31] The sample size for the majority of studies was small (range 22-289), with the exception of the 6 large national database studies which included several thousand patients. Detailed information about characteristics for each publication can be found in Table 6.

All of the studies included older adults (mean or median age >60), with only 2 reporting a median or mean age <60.[26,32] Most studies did not report on whether participants treated with various ablative treatments were felt to be medically operable or inoperable ($k = 8$)[19,21,23,26-28,30,32] or reported including both medically operable and inoperable patients ($k = 5$).[17,18,20,22,25] Only 2 studies reported on only medically operable individuals ($k = 2$)[15,29] and 3 studies reported on only medically inoperable individuals ($k = 3$).[16,24,31] None of the studies were conducted in Veterans. While most studies reported some information about tumor characteristics, there was no consistency across studies on which characteristics were reported. There was heterogeneity in reporting of tumor size (mean, median, or range provided) and cancer stage.

Interventions and Comparisons (Map 2)

In general, across studies, ablation was compared with surgery or radiotherapy. No studies of brachytherapy compared to surgery or radiotherapy (or other ablative therapies) were found. The interventions and comparisons for each study fell into 6 distinct comparison groups:

- ablation (type not specified or multiple types [cryoablation, laser ablation, radiofrequency ablation, microwave ablation] combined) versus radiotherapy ($k = 3$)[27,28,32];
- radiofrequency ablation versus radiotherapy ($k = 3$)[25,30,31];
- ablation (type not specified or multiple types combined) versus surgery ($k = 2$)[24,29];
- microwave ablation versus surgery ($k = 4$)[18,21,23,26];
- radiofrequency ablation versus surgery ($k = 4$)[15-17,21];
- radiotherapy versus radiofrequency ablation versus surgery ($k = 2$).[19,22]

Figure 3 shows the outcomes reported by comparisons made, and Figure 4 shows the outcomes reported, comparisons made, type of data used, and sample size for each publication.

Outcomes (Map 3)

With respect to outcomes, all publications reported overall survival ($k = 18$), most reported on local or regional recurrence ($k = 12$) and adverse events ($k = 11$), while fewer reported on lung-cancer-specific survival ($k = 8$) or distant recurrence ($k = 7$). We did not identify any publications that reported on quality of life. Figure 3 shows the outcomes that were reported by comparison group. A detailed breakdown of outcomes by study can be found in Table 7, and a detailed breakdown of specific adverse events reported by study can be found in Table 8.

Figure 2. KQ3 Literature Flowchart

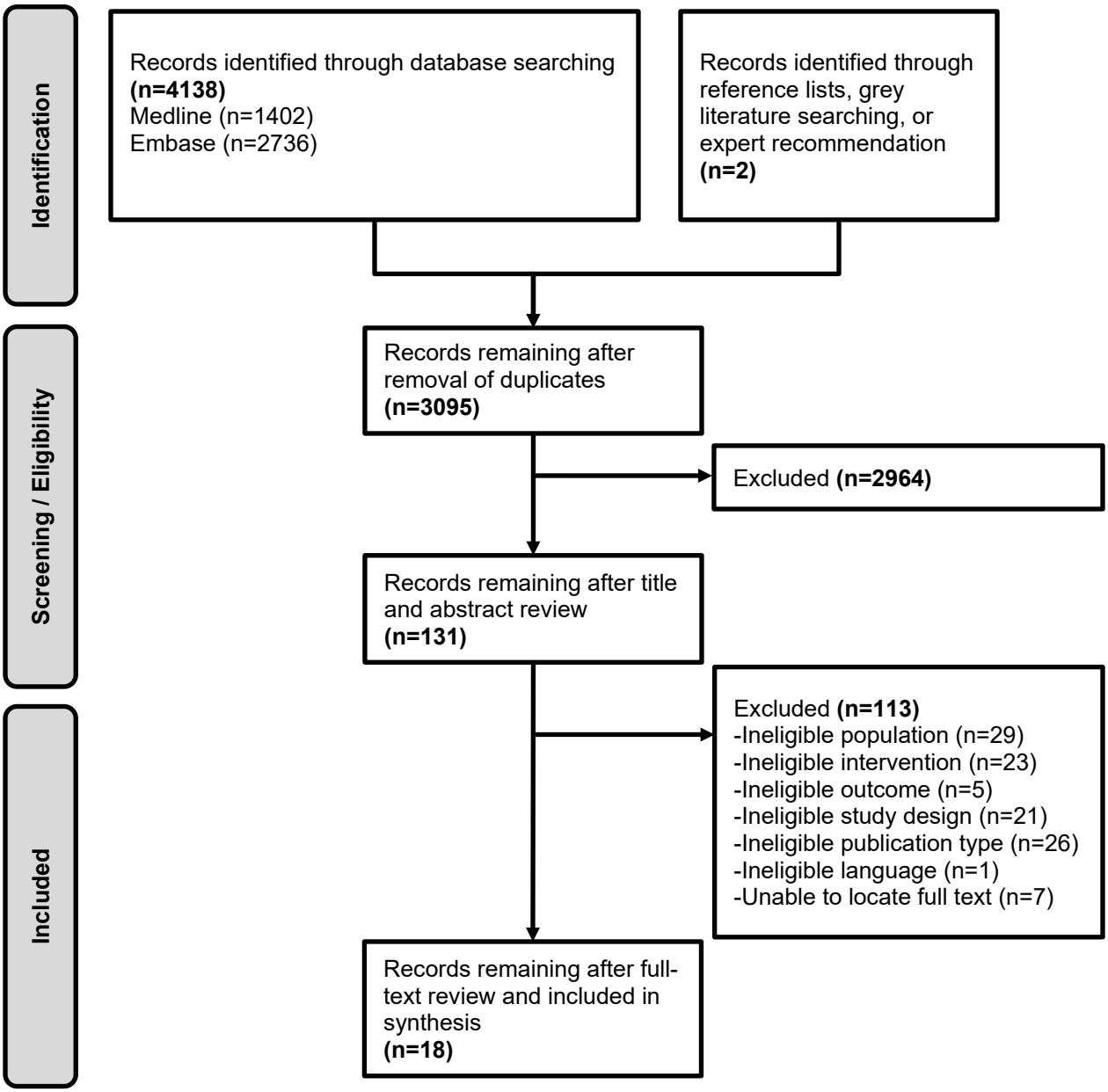

Table 6. Detailed Characteristics for Eligible Publications for Key Question 3

Author, Year	Characteristics				Comparisons Analyzed							Interventions Included						
	Country	Single-site Administrative Data	Multi-site Administrative Data	National Database	Ablation (Combined) vs Radiotherapy	Radiofrequency Ablation vs Radiotherapy	Ablation (Combined) vs Surgery	Microwave vs Surgery	Radiofrequency Ablation vs Surgery	Radiotherapy vs Radiofrequency Ablation vs Surgery	SBRT/SABR	Ablation (Not Specified)	Cryoablation	Radiofrequency Ablation	Microwave Ablation	Laser Ablation	Surgery
Ager, 2019[27]	US			✓*	✓						✓	✓	✓			✓	
Alexander, 2011[15]	US	✓							✓					✓			✓
Ambrogi, 2015[16]	Italy	✓							✓					✓			✓
Baine, 2019[28]	US			✓*	✓						✓		✓			✓	
Hsie, 2009[17]	US	✓							✓					✓			✓
Hu, 2021[18]	China	✓						✓							✓		✓
Iguchi, 2020[19]	Japan	✓								✓	✓			✓			✓
Kim, 2012[20]	South Korea	✓							✓					✓			✓
Kwan, 2014[29]	US			✓†			✓					✓					✓
Lam, 2018[30]	US			✓*		✓					✓			✓			
Li, 2021[31]	US			✓†		✓					✓			✓			
Mendogni, 2020[21]	Italy	✓						✓							✓		✓
Ochiai, 2015[25]	Japan		✓			✓					✓			✓			
Safi, 2015[22]	Ger-many	✓								✓	✓			✓			✓
Uhlig, 2018[32]	US			✓*	✓						✓		✓	✓		✓	
Wang, 2018[23]	China	✓						✓							✓		✓
Yao, 2018[26]	China		✓					✓							✓		✓
Zemlyak, 2010[24]	US	✓					✓						✓	✓			✓

Notes. *National Cancer Database (NCDB)
†Surveillance, Epidemiology and End-Results Database (SEER)

Figure 3. Outcomes Reported by Comparisons

	Overall Survival	Lung-cancer-specific Survival	Local/ Regional Recurrence	Systemic/ Distant Recurrence	Any Adverse Events	Quality of Life
Ablation (combined) vs Radiotherapy (*k*=3)	3	0	0	0	1	0
RFA vs Radiotherapy (*k*=3)	3	1	1	1	1	0
Ablation (combined) vs Surgery (*k*=2)	2	2	1	1	1	0
MWA vs Surgery (*k*=4)	4	3	4	2	3	0
RFA vs Surgery (*k*=4)	4	2	4	3	3	0
Radiotherapy vs RFA vs Surgery (*k*=2)	2	2	4	3	3	0

Notes. Combined indicates authors reported on outcomes based on different types of ablative therapy and not separately by specific ablative therapies.
Abbreviations. MWA=microwave ablation; RFA=radiofrequency ablation.

Figure 4. Evidence Map of Publications Reporting Ablation versus Radiotherapy or Ablation versus Surgery

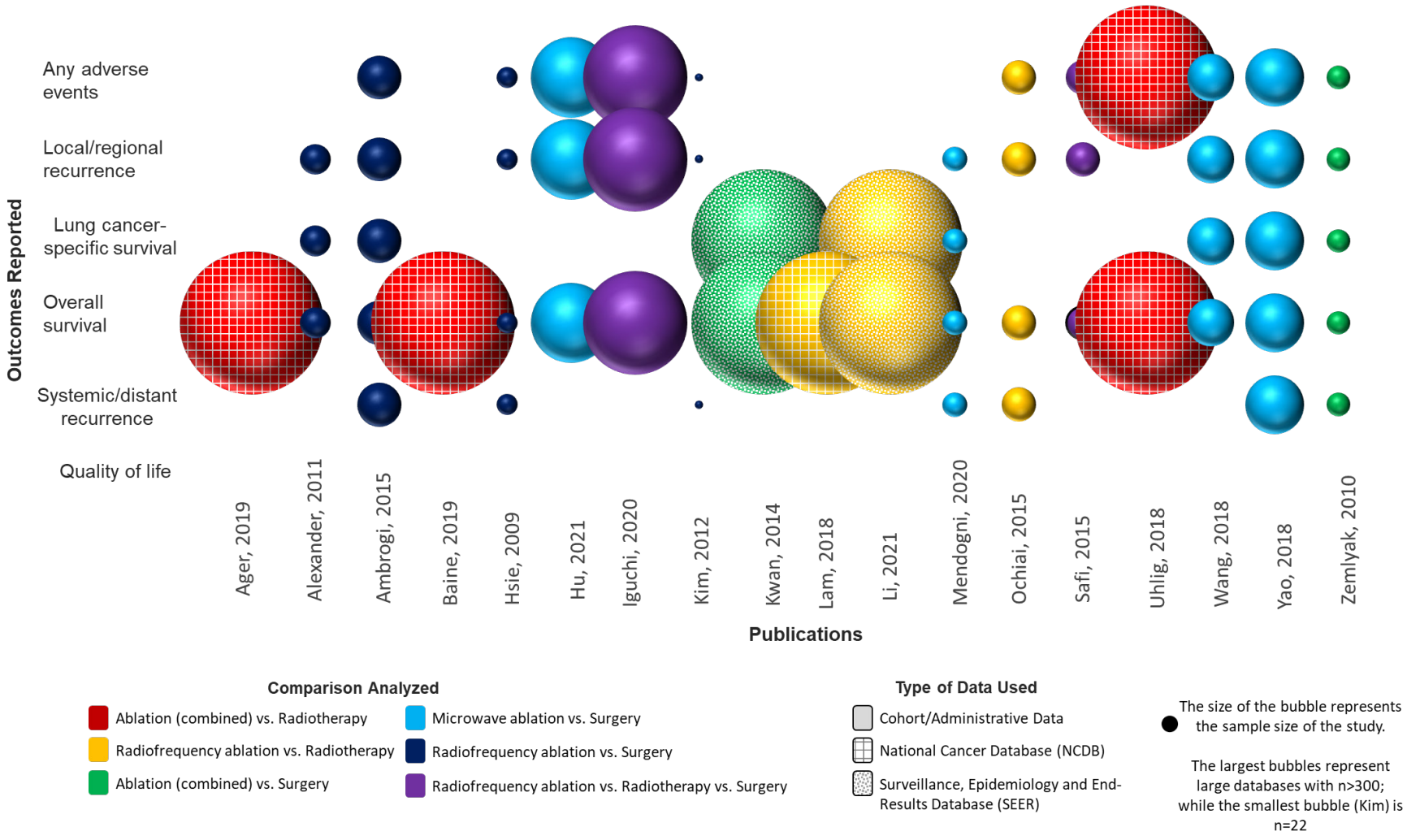

Table 7. Outcomes Reported by Eligible Publications for Key Question 3

Author, Year	Overall Survival	Lung-cancer-specific Survival	Local/Regional Recurrence	Systemic/Distant Recurrence	Any Adverse Events	Quality of Life	Short-term Cardiovascular Complications	Short-term Respiratory Complications	Long-term Respiratory Complications	Hospital Readmissions
Ager, 2019[27]	✓									
Alexander, 2011[15]	✓	✓	✓							
Ambrogi, 2015[16]	✓	✓	✓	✓	✓		✓	✓		
Baine, 2019[28]	✓									
Hsie, 2009[17]	✓		✓	✓	✓			✓		
Hu, 2021[18]	✓		✓		✓		✓	✓		
Iguchi, 2020[19]	✓		✓		✓		✓	✓		
Kim, 2012[20]	✓		✓	✓	✓			✓		
Kwan, 2014[29]	✓	✓								
Lam, 2018[30]	✓									
Li, 2021[31]	✓	✓								
Mendogni, 2020[21]	✓	✓	✓	✓						
Ochiai, 2015[25]	✓		✓	✓	✓			✓		
Safi, 2015[22]	✓		✓		✓		✓	✓	✓	✓
Uhlig, 2018[32]	✓				✓					✓
Wang, 2018[23]	✓	✓	✓		✓			✓		
Yao, 2018[26]	✓	✓	✓	✓	✓		✓	✓		
Zemlyak, 2010[24]	✓	✓	✓	✓	✓			✓		

Table 8. Specific Adverse Events Reported by Eligible Publications for Key Question 3

Author, Year	Short-term Cardiovascular Adverse Events							Short-term Respiratory Adverse Events								Long-term Respiratory Adverse Events				
	Atrial Fibrillation	*Pulmonary Arterial Thrombosis*	*Myocardial Ischemia*	*Heart Failure*	*Pulmonary Embolism*	*Myocardial Infarction*	*Cardiac Arrest*	*Pneumonia*	*Chest Tube*	*Pneumothorax*	*Pleural Effusion*	*Pneumonitis*	*Respiratory Failure*	*Hemothorax*	*Air Leak*	*Pneumonia*	*Dyspnea*	*Pleural Effusion*	*Pneumonitis*	*Hemothorax*
Ager, 2019[27]																				
Alexander, 2011[15]																				
Ambrogi, 2015[16]	✓									✓										
Baine, 2019[28]																				
Hsie, 2009[17]										✓										
Hu, 2021[18]	✓							✓	✓	✓	✓		✓							
Iguchi, 2020[19]		✓								✓	✓	✓								
Kim, 2012[20]										✓										
Kwan, 2014[29]																				
Lam, 2018[30]																				
Li, 2021[31]																				
Mendogni, 2020[21]																				
Ochiai, 2015[25]										✓	✓									
Safi, 2015[22]	✓								✓	✓	✓			✓				✓	✓	✓
Uhlig, 2018[32]																				
Wang, 2018[23]										✓	✓		✓							
Yao, 2018[26]	✓		✓	✓						✓	✓		✓							
Zemlyak, 2010[24]										✓	✓									

DISCUSSION

KEY MESSAGES

Key Questions 1 and 2

- Based on pooled data from the STARS and ROSEL trials comparing SABR/SBRT versus surgery, the evidence for 3-year survival, 3-year recurrence-free survival, quality of life, and adverse events is very uncertain (very low certainty of evidence).
    - Only 2 randomized trials, STARS and ROSEL, were identified that evaluated the role of SABR/SBRT compared to surgery for patients with medically operable stage I non-small cell lung cancer; both were terminated early due to lack of enrollment.
- No randomized trials were identified that examined if the benefits and harms of SABR/SBRT differ by patient characteristics, tumor characteristics, surgery characteristics, type of resection, or SBRT characteristics.
- There is an urgent need for randomized controlled trials to examine the comparative effectiveness of SABR/SBRT versus surgery for patients with medically operable stage I lung cancer.

We found insufficient evidence to inform the comparative effectiveness of SBRT/SABR versus surgery for stage I medically operable lung cancer. Our conclusions are based on 1 publication that pooled data from the STARS and ROSEL trials, which analyzed 58 persons with medically operable lung cancer (31 in the SABR group and 27 in the surgery group).[13] Both trials were terminated early due to low accrual rates over a 5-year time period (2008-2013). One additional study of 22 individuals randomly assigned to SABR ($N = 11$) and surgery ($N = 11$) over a median follow-up of 42 months evaluated quality of life using the EORTC QLQ-C30, 13-item lung cancer supplement (LC-13), and EQ-5D, which were administered at baseline, 3, 6, 12, 18, and 24 months.[14]

Based on these 2 studies, we have very low certainty in the comparative effectiveness of SABR versus surgery for the following outcomes: 3-year overall survival, 3-year recurrence-free survival, adverse events, and quality of life. Of the 27 patients who received surgery, 19 had open lobectomies, 5 had video-assisted thoracotomy lobectomies, 1 had video-assisted thoracotomy biopsy (mediastinal lymph node biopsy positive for metastatic lung cancer), 1 had open wedge resection (benign lung nodule), and 1 had an aborted resection during the surgery due to disease progression. Our very low certainty in the pooled estimates is based on concerns of performance and detection bias across the 2 trials, very small number of events in the 2 intervention groups (only 7 total deaths over 3 years), and low rates of minimally invasive surgical resection in the surgery arm (indirectness). Therefore, there is insufficient evidence (very low certainty) of the effects of SABR versus surgery.

While the evidence base was very sparse and deemed insufficient to address the comparative effectiveness of SBRT versus surgery, we found no data evaluating KQ2: *ie,* whether benefits and harms of SBRT compared with surgery differed by patient, tumor characteristics, surgery, or SBRT characteristics. These characteristics are important as clinical decisions often include these factors, and variation in these characteristics may confound findings from observational studies.

Randomized trials, including the ongoing VA Cooperative Studies Program VALOR trial,[6] are unlikely to be of sufficient size and design to adequately address all of these potential effect modifiers. However, researchers should include these components in future study designs and analyses.

These findings must be interpreted in the context of a large body of observational studies that have tried to address this question.[33] An important limitation of observational studies is that selection bias or confounding by indication may lead to inaccurate estimations of treatment effects. Confounding by indication is defined as a bias in the treatment-related outcome relationship due to the clinical reasons for the treatment. The indication for the treatment is based on physician and patient perceptions of disease severity and prognosis, including the presumed therapeutic effect of the intervention.[34] One approach to attempt to reduce this bias is the use of propensity-matched comparisons.

In the absence of evidence from randomized trials, investigators conducted a follow-up study of the STARS trial that used propensity matching.[35] This study was excluded during the full-text review process since it did not meet our required study design criteria for a RCT. In this single-center prospective observational study, the SABR group was re-accrued (using a revised STARS protocol) to allow for a larger sample size. Participants were then compared to a cohort of individuals that underwent video-assisted thorascopic surgical lobectomy with mediastinal lymph node dissection (VATS L-MLND) using a protocol-specified propensity-matched comparison. Propensity matching was performed for the following covariates: age, tumor, histology, performance status, and the interaction of age and sex. The following outcomes were reported: overall survival at 3 and 5 years, progression-free survival, cancer-specific survival rates, patterns of failure, predictive value of PET scans, local recurrence-free survival, and incidence of grade 3 or worse toxicity. Overall, 10 deaths occurred, and 15 patients developed progression in the SABR group over a median follow up of 5.1 years. In the surgery group, there were 15 deaths and 6 recurrences or distant metastases. The authors reported that overall survival at 3 years in the SABR group was 91% (95% CI [85%, 98%]) compared with 91% (95% CI [76%, 98%]) in the propensity-matched VATS-LMND cohort. Furthermore, overall survival at 5 years in the SABR cohort was 87% (95% CI [79%, 95%]) compared with 84% (95% CI [76%, 93%]) in the surgery cohort. Based on these results, SABR was reported to be non-inferior to VATS-MLND for operable stage IA NSCLC.

The authors acknowledged that propensity score matching was performed only for known potential variables. Thus, there may still be bias due to residual confounding from unknown variables for which matching was not performed. Additional limitations as outlined by the authors included persistent concerns about selection bias of patients enrolled into the revised STARS study due to lack of randomization, and concerns about determination of medical operability since the surgical cohort was not treated under a fixed protocol. Notwithstanding the results showing similar outcomes for these 2 interventions suggesting that SBRT/SABR is equally effective as compared to surgery (specifically VATS L-MLND), there is an urgent need for randomized controlled trials examining the comparative effectiveness of these 2 treatment modalities to inform practitioners and patients of the optimal treatment for stage I medically operable lung cancer.

Key Question 3

- There are no RCTs of ablation therapies for stage I lung cancer. The following ablation therapies have been studied in non-randomized comparative studies: cryoablation, radiofrequency ablation, microwave ablation, and laser ablation. Radiofrequency ablation was the most commonly studied ablative therapy (k = 11).
- Six retrospective studies reported on ablation compared with SBRT/SABR:
    - Ablation (any type combined) versus SBRT/SABR (k = 3)
    - Radiofrequency ablation versus SBRT/SABR (k = 3)
- Ten retrospective studies reported on ablation compared with surgery:
    - Microwave ablation versus surgery (k = 4)
    - Radiofrequency ablation versus surgery (k = 4)
    - Ablation (any type combined) versus surgery (k = 2)
    - SBRT/SABR versus radiofrequency ablation versus surgery (k = 2)
- Two studies compared ablation with SBRT/SABR and surgery:
    - SBRT/SABR versus radiofrequency ablation versus surgery (k = 2)
- Most studies had 300 or fewer participants (k = 12) and were conducted in the US (k = 9), Europe (k = 3), China (k = 3), Japan (k = 2), and South Korea (k = 1), with the exception of 6 studies of administrative datasets (NCDB and SEER) and included 2,000-30,000 participants.
- The majority of studies reported on the following outcomes: overall survival (k = 18), disease-free survival (k = 8), local/regional recurrence (k = 12), and any adverse events (k = 11). No studies reported on quality of life.
- None of these studies were conducted in Veterans and most studies were conducted prior to widespread lung cancer screening.

Ablative therapies using thermal ablation (radiofrequency ablation, microwave ablation, and laser ablation), cryoablation, and brachytherapy are often used as modalities for palliative treatment or in individuals with inoperable cancers, but these therapies have increasingly been used in medically operable individuals with lung cancer.[36] Based on our evidence map, there were a limited number of comparative studies of ablative treatments versus surgery for lung cancer. Most of these studies did not specify medically operable patients and did not provide the stage of disease. Furthermore, studies commonly reported on ablation versus surgery or SBRT/SABR without providing data on specific ablative therapies and stratifying results by ablative technique. When individual studies of ablation were reported, the most common ablative therapy was radiofrequency ablation.

The majority of studies reported on overall and lung-cancer-specific survival as well as disease recurrence and treatment-related adverse events. For adverse events, most studies reported short-term respiratory complications (k = 10) or short-term cardiovascular complications (k = 5). Only 1 study reported long-term respiratory complications and 2 reported on hospital readmissions.

However, reporting of short-term versus long-term AEs was not well defined, and it was difficult to tell from the articles if there was a follow-up period in which adverse events were being recorded. There were no studies reporting on quality of life. Most studies did not specify medically operable patients and did not provide the stage of disease. Due to the heterogeneity of the studies with respect to patient populations (combing medically operable with non-medically operable patients), interventions (data not provided for specific ablative therapy), and study designs, we did not pool across studies and make inferences about effect size or overall certainty of evidence. Since several studies were using administrative datasets, there was also concern about "double counting."

This evidence map for ablative therapies provides an overview of the scientific evidence, gaps in current knowledge, and needs of future research using visual analysis and graphic illustrations to help facilitate interpretation of results. This provides valuable information to researchers and funding organizations, as future clinical trials of different ablative therapies in individuals with medically operable lung cancer are needed to help inform practitioners and patients about the optimal role for ablative therapies within the framework of more established therapies such as surgery and SBRT.

LIMITATIONS

We acknowledge the following limitations of this evidence review. The results for the pooled analysis of the trials comparing SABR versus surgery were obtained from a publication of a post-hoc analysis of the 2 trials that had been terminated early due to lack of enrollment. We did not independently extract or pool the results from the trials, as the primary data were provided from the principal investigator for only 1 of the 2 trials despite attempts to obtain the results for each study. Furthermore, we focused our comparative effectiveness review on randomized controlled trials, in discussion with our nominating partner and TEP members. While numerous observational studies exist, including studies that utilize propensity matching, such study designs have not adequately addressed questions about comparative effectiveness and harms.

For the evidence map, we included observational studies with a comparator arm to better understand how ablative therapies have been evaluated as compared to standard therapies. Some of the retrospective studies of administrative datasets may have had overlapping years for patient selection and individuals may have been "double counted" across studies. Furthermore, these studies did not clearly distinguish medically operable versus inoperable persons and provided limited reporting on how individuals were selected to receive specific treatments. In this evidence map, we also did not provide information on effect size, direction of effect, or assessment of quality of studies to limit misinterpretation or over reliance on these studies for decision-making. These limitations notwithstanding, the evidence map outlines the current landscape of studies that have compared various ablative treatment strategies to inform the research agenda for future clinical trials.

APPLICABILITY

None of the studies were specific to VA populations. The ongoing VALOR RCT,[6] funded by the VA Cooperative Studies Program (CSP #2005) aims to recruit 670 Veterans from at least 16 VA hospitals to compare stereotactic radiotherapy to standard lobectomy or segmentectomy for the treatment of medically operable, histologically confirmed, centrally or peripherally located stage I non-small cell lung cancers. Importantly, adequate recruitment and follow-up will be critical to

the success of this trial. Establishing equipoise and addressing patient treatment preferences will be an important barrier to overcome.[37] As management of lung cancer patients requires extensive multidisciplinary care and follow-up, interventions that support "buy-in" from different subspecialists and opportunities for shared decision-making as well as sustained efforts to promote recruitment into the trial will also be critical.

FUTURE RESEARCH

The results of our systematic review underscore the recognition that data from randomized controlled trials, especially that of the VA Cooperative Study VALOR,[6] are critically needed to inform decisions around primary treatment for stage I lung cancer. The scarcity of randomized trial data is a major limitation in understanding the comparative effectiveness of different treatment strategies. This is particularly relevant given that the updated recommendations for expanded lung cancer screening incorporate surgical candidacy or willingness to undergo surgery as a prerequisite for offering screening.

Future studies should:

- Use consistent terminology or definitions for medically operable disease using standardized protocols for enrollment to further minimize selection bias or confounding by indication and provider bias for enrollment.
- Ensure adequate experience and training in the performance of minimally invasive surgery and ablative therapies.
- Ensure adequate enrollment and follow-up to have adequate sample size to detect clinically meaningful differences in overall and cancer-specific survival, tumor-free progression, adverse effects, quality of life, and long-term side effects (using consistent definitions).
- Be pragmatic in design to ensure that studies address the range of patients, tumors, and interventions under clinical consideration for individuals with newly diagnosed lung cancer (especially screen detected).
- Recruit patient engagement groups to understand barriers and seek solutions to randomization in trials of these vastly different treatments, and examine values and preferences, acceptability, and feasibility.
- Assess potential expansion of treatment options for stage I lung cancer to include SABR/SBRT and/or ablative therapies (potentially as a 3-arm trial).
- Explore how inclusion of screen-detected lesions would influence screening and treatment decisions and resultant net benefits. This includes use of less invasive therapies for small, indolent lung cancers among older sicker adults who would otherwise not have been candidates for screening or subsequent treatment.

CONCLUSIONS

In summary, the evidence is uncertain on the comparative effectiveness and harms of surgery versus SBRT/SABR for adults with medically operable lung cancer. Lung cancer is among the most common and lethal cancers globally. Those with early stage, especially cancers detected by

low-dose CT screening, have the highest chance for effective therapies and mortality reduction. While surgery has been commonly considered the treatment strategy of choice for medically operable disease, stereotactic radiotherapy has emerged as an alternative treatment strategy. Given current evidence uncertainty, overall disease burden, and the growing role of lung cancer screening, robust randomized controlled trial results are needed. Furthermore, the field of ablative therapies continues to innovate and expand and is becoming more widely studied. There is a critical need for robust evidence on comparative treatment effects as well as patient preferences and values to inform the management of patients with medically operable stage I non-small cell lung cancer.

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