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.

# 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 |

# EXECUTIVE SUMMARY

## Key Findings

### 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 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)?
- 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 COE).
    - 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.

### 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?
- No RCTs examined ablation therapies for stage 1 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 ($k = 1$) except for 6 studies of administrative datasets (NCDB and SEER) that 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.

## INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the United States (US). 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. Within the Veterans Health Administration (VA), approximately 8,000 Veterans are diagnosed with and treated for lung cancer every year. Surgery, including lobectomy, segmentectomy, wedge resection, and sleeve resection with or without the use of minimally invasive approaches, has been considered the standard of care for individuals with early-stage lung cancer who are deemed to be medically operable. Stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) are frequently offered to individuals considered to be medically inoperable for various reasons (due to advanced age or with comorbidities that place them at high risk for severe perioperative complications). Promising results with SBRT/SABR in patients deemed to be medically inoperable have led to studies evaluating the efficacy and long-term outcomes of this therapy as an alternative to surgery in medically operable patients. These results raise questions about definitive treatment options for early-stage lung cancer.

This review addresses important questions regarding the comparative effectiveness of surgery versus SBRT/SABR as well as the current body of evidence for ablative therapies such as radiofrequency ablation, cryoablation, microwave ablation, laser ablation, and brachytherapy in the management of medically operable stage I lung cancer. This topic was nominated by the National Radiation Oncology Program. Additionally, this review provides the background rationale for an ongoing VA Cooperative Study, a randomized trial of surgery versus SBRT (NCT02984761). Findings will be used to inform use of treatment modalities in patients with stage I lung cancer who are deemed medically operable.

The Key Questions (KQs) for this review are:

- 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?

# METHODS

## Data Sources and Searches

Two search strategies were developed to address the KQs. We searched MEDLINE and Embase from inception to September 2022. We supplemented these searches with a review of relevant systematic review bibliographies. We limited the searches to published and indexed articles involving human subjects available in the English language.

## Study Selection

Based on discussion with our nominating partner and technical expert panel members, we focused on randomized controlled trials for KQs 1 and 2 because prior work that relied on observational studies (even with the use of statistical techniques to adjust for confounding) was deemed inadequate to accurately inform comparative effectiveness and harms. As the goal for KQ3 was revised to include an evidence map of comparative studies of ablative therapies, our study eligibility criteria included randomized trials or observational studies with a comparator arm (KQ3) that evaluated ablation therapy compared with surgery (or SBRT/SABR) or other ablation therapies. Using prespecified inclusion/exclusion criteria, titles and abstracts were screened independently by at least 1 reviewer from the systematic review team 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.

## Data Abstraction and Assessment

Data from eligible studies were abstracted by 1 reviewer and verified by a second reviewer. Any disagreements were resolved by consensus between reviewers or arbitrated by the systematic review authors. 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.

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. No formal risk of bias assessment was performed for studies meeting eligibility criteria.

### Synthesis

For KQs 1 and 2, we identified publications 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 overall survival, lung-cancer-specific survival, quality of life, and adverse events of grade 2 or higher, according to the GRADE approach. One author independently rated the certainty of evidence for each outcome, and any disagreement was resolved through group consensus with the team.

For KQ3, because of the heterogeneity of identified studies, no formal synthesis of study results was performed. To summarize the evidence on ablation therapies, we provided a descriptive overview of the data in a narrative review and provided visual graphics, including tables and a bubble plot, to summarize the key features of the studies. We mapped the results by intervention versus comparison, types of outcomes, and sources of data (*eg,* populations).

## RESULTS

### Results of Literature Search

For KQ1, 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. 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.

For KQ3, 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.

### Summary of Results for Key Questions

#### *KQ1*

One publication pooled data from 2 trials ($N = 58$): 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 and 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 second publication reported quality of life data from the ROSEL trial (N = 19). Both publications were judged to have “some concerns” for risk of bias. Across outcomes, there is

insufficient evidence on the comparative effectiveness of SBRT/SABR versus surgery for overall survival at 3 years, recurrence-free survival at 3 years, grade ≥ 3 adverse events, and quality of life.

### *KQ3*

Radiofrequency ablation was the most commonly studied ablative therapy. In general, across studies, ablation was compared with surgery or radiotherapy. The majority of publications were single-site retrospective cohort studies. Six publications used national US databases, including the National Cancer Database (NCDB) and the Surveillance, Epidemiology and End-Results Database (SEER). Most studies were small (range 22-289 patients) with the exception of the 6 large national database studies which included several thousand patients (range 2,000-30,000 patients). All the studies included older adults and most studies did not report on whether participants were formally assessed, at the time of treatment, as medically operable or inoperable. Two studies reported on only medically operable individuals. None of the studies were conducted in Veterans. While most studies provided some information about tumor characteristics, there was no consistency across studies on which characteristics were reported. There was variation in reporting of tumor size (mean, median, or range provided) and cancer stage. 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 ($k = 7$).

## DISCUSSION

### Key Findings and Strength of Evidence

Our systematic review has several key findings and limitations. The main limitations and key findings are based on the sparseness and low overall certainty of existing evidence. We found insufficient evidence to inform the comparative effectiveness of SBRT/SABR versus surgery for stage I medically operable lung cancer. Based on 2 studies, we have very low certainty of the comparative effectiveness of SABR versus surgery for the following outcomes: 3-year survival, 3-year recurrence free survival, adverse events, and quality of life. Our very low certainty in the estimates is based on concerns of performance bias, detection bias, and indirectness with 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. The 2 identified RCTs did not employ video-assisted or robotic surgical approaches and thus may not be representative of harms or quality of life from contemporary less invasive surgical approaches.

We found no data evaluating 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.

The comparative effectiveness (and harms) of 2 treatments is ideally based on a randomized trial designed to minimize selection bias as well as performance and detection bias, which can lead to an inaccurate estimate of treatment effects. Several observational studies comparing patient outcomes with surgery versus SBRT have attempted to adjust for confounding by using statistical techniques. One study, outlined below, attempted to use a revised protocol of the STARS trial to re-accrue patients as a prospective single-center study cohort and used propensity

matching to adjust for prognostic baseline differences between the groups. Participants were 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. 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 and 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. 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. Based on these findings, the authors concluded that SABR was non-inferior to VATS-MLND for operable stage IA NSCLC. However, the authors acknowledged persistent concerns about selection bias due to lack of randomization and about determination of medical operability since the surgical cohort was not treated under a fixed protocol.

Based on our evidence map, we found no RCTS of ablative therapies for stage I lung cancer. We found only a limited number of comparative studies of ablative treatments versus surgery for lung cancer. All were observational and many were small single-center reports. While ablative therapies are widely used for palliative treatment in many cancer types, especially among individuals with metastatic disease, there are few reports of these therapies used as potentially definitive therapy in localized lung cancer. Most studies did not specify medically operable patients and did not provide the stage of disease. Because the heterogeneity of the studies with respect to patient populations, interventions, and study designs, we did not pool across studies and make inferences about effect size or overall certainty of evidence. Furthermore, studies commonly reported on ablation versus surgery or SBRT/SABR without providing data on specific ablative therapies. Large studies using administrative data are unlikely to capture information on medical operability. 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 with heterogenous reporting of treatment-related adverse events, and no data on quality of life. None of the studies provided information on patient, tumor, or treatment characteristics likely of importance for decision-making.

## Applicability

Many of the reported studies were conducted prior to widespread lung cancer screening with low-dose CT scanning, which may result in detection of smaller lesions and concerns for overtreatment. None of the studies were specific to VA populations. The ongoing VALOR (Veterans Affairs Lung Cancer Surgery or Stereotactic Radiotherapy) RCT, 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.

## Future Research

The results of our systematic review underscore the recognition that data from randomized controlled trials, especially that of the VA VALOR Cooperative Study, 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, we found insufficient evidence on the comparative effectiveness and harms of surgery versus SBRT/SABR for adults with medically operatable stage I lung cancer. Furthermore, the field of ablative therapies continues to innovate and is becoming more widely studied. Because of treatment outcome uncertainty, the increased implementation of lung cancer screening programs, and the fact that lung cancer remains one of the most common and lethal cancers globally, there is a critical need for robust evidence on comparative treatment effects. Additionally, information is needed on patient preferences and values to inform the management of patients with medically operable stage I non-small cell lung cancer.