Table S1-1 Definition of a clinically meaningful difference

| Variable                          | Units       | 2x meaningfully worse | Meaningfully worse | Somewhat worse | Similar | Somewhat better | Meaningfully better | 2x meaningfully better |
|-----------------------------------|-------------|-----------------------|-------------------|---------------|---------|----------------|---------------------|-----------------------|
| 90-day mortality                  | %           | ↓↓↓                   | ↓↓               | ↓              | =       | ↓              | ↑                   | ↑↑                   |
| 90-day grade ≥3 morbidity/toxicity| %           | Δ ≥20                 | Δ ≥10             | Δ ≥5           | =       | Δ ≥5           | Δ ≥10               | Δ ≥20                 |
| QOL (all domains)                 | Norm scale  | Δ ≥20                 | Δ ≥10             | Δ ≥5           | =       | Δ ≥5           | Δ ≥10               | Δ ≥20                 |
| FEV1% (pre vs. post), healthy patient | Absol FEV1% | Δ ≥20                 | Δ ≥10             | Δ ≥5           | =       | Δ ≥5           | Δ ≥10               | Δ ≥20                 |
| FEV1% (pre vs. post), severe COPD | Absol FEV1% | Δ ≥20                 | Δ ≥10             | Δ ≥5           | =       | Δ ≥5           | Δ ≥10               | Δ ≥20                 |
| 5-year OS                         | %           | Δ ≥20                 | Δ ≥10             | Δ ≥5           | =       | Δ ≥5           | Δ ≥10               | Δ ≥20                 |
| 5-year LCSS                       | %           | Δ ≥20                 | Δ ≥10             | Δ ≥5           | =       | Δ ≥5           | Δ ≥10               | Δ ≥20                 |
| FFR                               | %*          | Δ ≥20                 | Δ ≥10             | Δ ≥5           | =       | Δ ≥5           | Δ ≥10               | Δ ≥20                 |
| LR FFR                            | %*          | Δ ≥20                 | Δ ≥10             | Δ ≥5           | =       | Δ ≥5           | Δ ≥10               | Δ ≥20                 |

The comparison is the delta between one treatment approach and another (e.g., lobectomy vs. wedge).

The process to define the threshold for a “clinically meaningful” difference: the writing panel reviewed literature, discussed potential thresholds and arrived at a consensus at the outset for outcomes in which a formal standard is not available (1). For quality-of-life domains generally accepted thresholds for clinically meaningful differences have been defined (2-8). For FEV1 in healthy patients it was considered that ≥80% is regarded as normal, that dyspnea on exertion is rarely noted for FEV1 ≥60%, and that most patients with lung cancer are not engaged in high level strenuous activity. For outcomes lacking a formal standard, the panel considered a level at which a difference would begin to factor into decision-making, taking into account the impact on a patient and uncertainties (e.g., definition of toxicity, recurrence).
**Figure S1-1 Decision guide for healthy patients—SBRT/ablation vs. open surgery.**

Decision guide for a generally healthy patient with a typical stage I lung cancer. The reference (for improvement or worsening) is the treatment in parentheses.

- Δ FEV1, change in FEV1 ≥ 6 months; Abl, ablation (any thermal technique); Conf, confidence in the evidence; FFR, freedom from recurrence (only recurrence counts as an event); LCSS, lung cancer specific survival (only a death due to lung cancer counts as an event); L, lobectomy; LR-FFR, locoregional freedom from recurrence; NSCLC, non-small cell lung cancer; OS, overall survival; QOL, quality of life; SBRT, stereotactic body radiotherapy; SL, sublobar resection; Seg, segmentectomy; W, wedge.
Figure S1-2 Decision guide for older patients—SBRT/ablation vs. open surgery.

Decision guide for an older patient with a typical stage I lung cancer. The reference (for improvement or worsening) is the treatment in parentheses.

Δ FEV1, change in FEV1 ≥6 months; Abl, ablation (any thermal technique); Conf, confidence in the evidence; FFR, freedom from recurrence (only recurrence counts as an event); LCSS, lung cancer specific survival (only a death due to lung cancer counts as an event); L, lobectomy; LR-FFR, locoregional freedom from recurrence; NSCLC, non-small cell lung cancer; OS, overall survival; PS, performance status; QOL, quality of life; SBRT, stereotactic body radiotherapy; SL, sublobar resection; Seg, segmentectomy; W, wedge.

| Nuances |
| --- |
| Preferences affect how outcomes are weighed |
| ↑ age (↑ frailty) accentuates short-term differences, diminishes long-term differences |
| Aggressive tumors may accentuate long-term differences |

| Key selection factors: |
| --- |
| • Patient factors affecting 90-day outcomes; PS/robustness probably more relevant than age |
| • Tumor and technical factors influencing treatment effectiveness |
| • Tumor aggressiveness |

| Effect | Confidence in Consistency of Data |
| --- | --- |
| Mean/meaningful improvement | ++++ Very High |
| Somewhat better | +++ High |
| Somewhat worse | ++ Moderate |
| Mean/meaningful worsening | + Low |
| Very meaningful worsening | Very Low |

| Older Patients, cl (8th Ed) NSCLC |
| --- |
| SBRT / ABL v Open Surgery |

| Intermediate (1-2 year) Outcomes |
| --- |
| SBRT (v Lobe/SL) | ABL (v SL) | ABL (v SBRT) |
| Δ FEV1 | Effect | Conf | Effect | Conf | Effect | Conf |
| Dyspnea | - | - | - | - | - | - |
| QOL | ↑↑ | ++ | ↑ | 0 | ↓ | 0 |
| Pain | ↑ | 0 | ↑ | 0 | ↓ | 0 |

| Long-Term (5-year) Outcomes |
| --- |
| SBRT (v Lobe/SL) | ABL (v SL) | ABL (v SBRT) |
| OS | ↓↓ | + | ↓↓↓ | + |
| LCSS | ↓↓ | + | ↓↓↓ | + |
| FFR | - | - | - | - |
| LR-FFR | - | - | - | - |

Legend

![Legend Image]
Figure S1-3 Decision guide for compromised patients—SBRT/ablation vs. open surgery.

Decision guide for a compromised patient with a typical Stage I lung cancer. The reference (for improvement or worsening) is the treatment in parentheses.

‘a’, data not parsed by resection extent (segment vs. wedge).
Δ FEV1, change in FEV1 ≥6 months; Abl, ablation (any thermal technique); Conf, confidence in the evidence; FFR, freedom from recurrence (only recurrence counts as an event); LCSS, lung cancer specific survival (only a death due to lung cancer counts as an event); L, lobectomy; LR-FFR, locoregional freedom from recurrence; NSCLC, non-small cell lung cancer; OS, overall survival; QOL, quality of life; SBRT, stereotactic body radiotherapy; SL, sublobar resection; Seg, segmentectomy; W, wedge.
## Appendix 1-1 PICO questions

**Primary study questions, PICO format (population, intervention, comparator, outcomes)**

| Study characteristic | Inclusion criteria | Exclusion criteria |
|----------------------|-------------------|-------------------|
| **1. What are the short-term outcomes in patients with cIA NSCLC undergoing lobectomy compared to either segmentectomy or wedge resection?** | | |
| **Population** | Patients with cIA* NSCLC (treatment naïve) | Not NSCLC, not cIA*, not resected, other outcomes |
| **Interventions** | Lobectomy (VATS or open) | |
| **Comparators** | Segmentectomy, wedge resection, sublobar resection (VATS or open) | |
| **Outcomes** | Short-term mortality, morbidity, pain, QOL | |
| **Study design** | RCT, adjusted NRC, guidelines, systematic reviews and meta-analyses; observational studies if RCT or NRC not available | Not meeting study design criteria |
| **2. What are the long-term outcomes in patients with cIA NSCLC undergoing lobectomy compared to either segmentectomy or wedge resection?** | | |
| **Population** | Patients with cIA* NSCLC (treatment naïve) | Not NSCLC, not cIA*, not resected, other outcomes |
| **Interventions** | Lobectomy (VATS or open) | |
| **Comparators** | Segmentectomy, wedge resection, sublobar resection (VATS or Open) | |
| **Outcomes** | OS, LCSS, FFR, LR-FFR, DFS/RFS, PFTs, pain, QOL | |
| **Study design** | RCT, adjusted NRC, guideline, systematic reviews and meta-analyses; observational studies for endpoints of PFTs, Pain, QOL | Not meeting study design criteria |
| **3. What are the short-term outcomes in patients with cIA NSCLC undergoing SBRT compared to surgical resection (lobectomy, segmentectomy or wedge resection)?** | | |
| **Population** | Patients with cIA* NSCLC (treatment naïve) | Not NSCLC, not cIA*, not treated by resection or SBRT, other outcomes |
| **Interventions** | SBRT | |
| **Comparators** | Surgical resection (VATS or open, lobectomy or sublobar) | |
| **Outcomes** | Short-term mortality, toxicity/morbidity, pain, QOL | |
| **Study design** | RCT, adjusted NRC, guideline, systematic reviews and meta-analyses, observational studies if RCT or NRC not available | Not meeting study design criteria |
| **4. What are the long-term outcomes in patients with cIA NSCLC undergoing SBRT compared to surgical resection (lobectomy, segmentectomy or wedge resection)?** | | |
| **Population** | Patients with cIA* NSCLC (treatment naïve) | Not NSCLC, not cIA*, not treated by resection or SBRT, other outcomes |
| **Intervention** | SBRT | |
| **Comparators** | Surgical resection (VATS or open, lobectomy or sublobar) | |
| **Outcomes** | OS, LCSS, FFR, LR-FFR, DFS/RFS, PFTs, pain, QOL | |
| **Study design** | RCT, adjusted NRC, guideline, systematic reviews and meta-analyses; observational studies for endpoints of PFTs, pain, QOL | Not meeting study design criteria |
5. What are the short-term outcomes in patients with cIA NSCLC undergoing Ablation compared to surgical resection (lobectomy, segmentectomy or wedge resection)?

| Population | Patients with cIA* NSCLC (treatment naïve) | Not NSCLC, not cIA*, not treated by resection or ablation, other outcomes |
|------------|------------------------------------------|-----------------------------------------------------------------------|
| Interventions | Ablation (radiofrequency, microwave, cryotherapy, other) |                                                      |
| Comparators | Surgical resection (VATS or open, lobectomy or sublobar) |                                                      |
| Outcomes | Short-term mortality, toxicity/morbidity, pain, QOL |                                                      |
| Study design | RCT, adjusted NRC, guideline, systematic reviews and meta-analyses, observational studies if RCT or NRC not available | Not meeting study design criteria |

6. What are the long-term outcomes in patients with cIA NSCLC undergoing Ablation compared to surgical resection (lobectomy, segmentectomy or wedge resection)?

| Population | Patients with cIA* NSCLC (treatment naïve) | Not NSCLC, not cIA*, not treated by resection or ablation, other outcomes |
|------------|------------------------------------------|-----------------------------------------------------------------------|
| Interventions | Ablation (radiofrequency, microwave, cryotherapy, other) |                                                      |
| Comparators | Surgical resection (VATS or open, lobectomy or sublobar) |                                                      |
| Outcomes | OS, LCSS, FFR, LR-FFR, DFS/RFS, PFTs, Pain, QOL |                                                      |
| Study design | RCT, adjusted NRC, guideline, systematic reviews and meta-analyses; observational studies for endpoints of PFTs, pain, QOL | Not meeting study design criteria |

7. What are the short-term outcomes in patients with cIA NSCLC undergoing Ablation compared to SBRT?

| Population | Patients with cIA* NSCLC (treatment naïve) | Not NSCLC, not cIA*, not treated by SBRT or ablation, other outcomes |
|------------|------------------------------------------|-----------------------------------------------------------------------|
| Interventions | Ablation (radiofrequency, microwave, cryotherapy, other) |                                                      |
| Comparators | SBRT |                                                      |
| Outcomes | Short-term mortality, toxicity/morbidity, pain, QOL |                                                      |
| Study design | RCT, adjusted NRC, Guideline, systematic reviews and meta-analyses, observational studies if RCT or NRC not available | Not meeting study design criteria |

8. What are the long-term outcomes in patients with cIA NSCLC undergoing Ablation compared to SBRT?

| Population | Patients with cIA* NSCLC (treatment naïve) | Not NSCLC, not cIA*, not treated by SBRT or ablation, other outcomes |
|------------|------------------------------------------|-----------------------------------------------------------------------|
| Interventions | Ablation (radiofrequency, microwave, cryotherapy, other) |                                                      |
| Comparators | SBRT |                                                      |
| Outcomes | OS, LCSS, FFR, LR-FFR, DFS/RFS, PFTs, pain, QOL |                                                      |
| Study design | RCT, adjusted NRC, guideline, systematic reviews and meta-analyses; observational studies for endpoints of PFTs, Pain, QOL | Not meeting study design criteria |

* inclusion of stage II–IIIA allowed if included together with stage I; stage translated into 8th edition nomenclature as much as possible for consistency across studies and contemporary applicability.

DFS/RFS, disease/recurrence-free-survival; FFR, freedom-from-recurrence; LCSS, lung cancer specific survival; LR, loco-regional; NRC, non-randomized comparison; NSCLC, non-small cell lung cancer; OS, overall survival; PFT, pulmonary function tests; QOL, quality-of-life; RCT, randomized controlled trial; SBRT, stereotactic body radiotherapy; VATS, video-assisted thoracic surgery.

No formal study protocol was written beyond the PICO questions. This systematic review was not registered as such.
### Appendix 1-2 Search strategies and results

**For all Searches:**
Source: PubMed  
Filters: English, 2000-2021, journal article  
Initial Formal Searches: December 2020  
initial Ad Hoc searches: May 2020 to May 2021  
Date of Last formal update search: October 7, 2021  
Date of Last Ad Hoc update searches: October 2021

**Contacts with authors regarding details or ongoing studies:**
STEPS – Wentao Fang, Shanghai, China & Jun Wang, Beijing 4-23-2020  
CALGB 140503  Nassar Altorki, NY, USA  4-27-2020  
JCOG 1211  Kenji Suzuki, Japan  2-24-2020  
Yasuhiro Tsutani, Hiroshima, Japan 2-20-2020

**Additional information**
Further detail (full search lists, reasons for exclusion, etc.) can be provided by contacting the corresponding author.

#### Resection extent
![Diagram showing the process of search strategies and results]

**Search string**

("carcinoma, non small cell lung"[MeSH Terms] OR ("carcinoma non small cell lung"[All Fields] OR "carcinomas non small cell lung"[All Fields] OR "lung carcinoma non small cell"[All Fields] OR "Non-Small-Cell Lung Carcinomas"[All Fields] OR "Nonsmall Cell Lung Cancer"[All Fields] OR "non-small-cell lung carcinoma"[All Fields] OR "non small cell lung carcinoma"[All Fields] OR "carcinoma non small cell lung"[All Fields] OR "Non-Small Cell Lung Cancer"[All Fields])) AND ("early stage" OR "stage Ia") AND ("Pneumonectomy"[MeSH Terms] OR ("lobectom*"[All Fields] OR "pneumonectom*"[All Fields])) AND ("sublobar resection*"[Title/Abstract] OR "wedge resection*"[Title/Abstract] OR "segmentectom*"[Title/Abstract] OR "segment resection*"[Title/Abstract]).
Search string: QOL review:
("carcinoma, non small cell lung"[MeSH Terms] OR "carcinoma non small cell lung"[All Fields] OR "carcinomas non small cell lung"[All Fields] OR "lung carcinoma non small cell"[All Fields] OR "lung carcinomas non small cell"[All Fields] OR "Non-Small-Cell Lung Carcinomas"[All Fields] OR "Nonsmall Cell Lung Cancer"[All Fields] OR "non-small-cell lung carcinoma"[All Fields] OR "non-small-cell lung carcinoma"[All Fields] OR "canceroma non small cell lung"[All Fields] OR "canceroma non small cell lung"[All Fields] OR "Non-Small Cell Lung Cancer"[All Fields] AND ((journalarticle[Filter]) AND (english[Filter]))) OR (lung neoplasm[MeSH Terms]) AND ((("quality of life") OR ("qol")) OR ("pain")) OR (quality of life[MeSH Terms]) AND ((journalarticle[Filter]) AND (english[Filter])) AND ("ablation"[All Fields] OR "radiofrequency ablation"[All Fields] OR "radiofrequency ablation"[MeSH Terms] OR "catheter ablation"[MeSH Terms] OR "catheter ablation"[MeSH Terms] OR "catheter ablation"[MeSH Terms]) OR ("radiosurgery"[All Fields] OR "radiosurgery"[MeSH Terms] OR "SBRT"[All Fields] OR "Stereotactic body radiation therapy"[All Fields] OR "stereotactic radiosurgery"[All Fields]) OR ((("Pneumonectomy"[MeSH Terms] OR ("lobectomy"[All Fields] OR "pneumonectomy"[All Fields]))) OR ("sublobar resection"[Title/Abstract] OR "wedge resection"[Title/Abstract] OR "segmentectomy"[Title/Abstract] OR "segment resection"[Title/Abstract])).
Search string: SBRT review:
“carcinoma, non small cell lung”[MeSH Terms] OR “carcinoma non small cell lung”[All Fields] OR “carcinomas non small cell lung”[All Fields] OR “lung carcinoma non small cell”[All Fields] OR “lung carcinomas non small cell”[All Fields] OR “Non-Small-Cell Lung Carcinomas”[All Fields] OR “Nonsmall Cell Lung Cancer”[All Fields] OR “non-small-cell lung carcinoma”[All Fields] OR “non-small-cell lung carcinoma”[All Fields] OR “carcinoma non small cell lung”[All Fields] OR “Non-Small Cell Lung Cancer”[All Fields] AND “early stage”[All Fields] OR “stage1”[All Fields] OR “stage 1”[All Fields] OR “stage I”[All Fields] OR “stage Ia”[All Fields] OR “stage Ib”[All Fields] OR “ct1n0”[All Fields] OR “ct1a”[All Fields] OR “ct1b”[All Fields] OR “cT1a”[All Fields] OR “cT1b”[All Fields] AND (“radiosurgery”[All Fields] OR “radiosurgery”[MeSH Terms] OR “SBRT”[All Fields] OR “Stereotactic body radiation therapy”[All Fields] OR “stereotactic radiosurgery”[All Fields]) AND (“journal article”[Publication Type] AND “english”[Language]) AND (“journal article”[Publication Type] AND “english”[Language]).
Ablation

Search string: ablation review:
"carcinoma, non small cell lung"[MeSH Terms] OR "carcinoma non small cell lung"[All Fields] OR "carcinomas non small cell lung"[All Fields] OR "lung carcinoma non small cell"[All Fields] OR "lung carcinomas non small cell"[All Fields] OR "Non-Small-Cell Lung Carcinomas"[All Fields] OR "Nonsmall Cell Lung Cancer"[All Fields] OR "non-small-cell lung carcinoma"[All Fields] OR "non-small-cell lung carcinoma"[All Fields] OR "Non-Small Cell Lung Cancer"[All Fields] OR "Non-Small-Cell Lung Carcinomas"[All Fields] OR "Nonsmall Cell Lung Cancer"[All Fields] OR "non-small-cell lung carcinoma"[All Fields] OR "non-small-cell lung carcinoma"[All Fields] AND "early stage"[All Fields] OR "stage1"[All Fields] OR "stage 1"[All Fields] OR "stage I"[All Fields] OR "stage Ia"[All Fields] OR "stage Ib"[All Fields] OR "ct1n0"[All Fields] OR "ct1a"[All Fields] OR "ct1b"[All Fields] OR "cT1a"[All Fields] OR "cT1b"[All Fields] OR "cTT"[All Fields] OR "cT1a"[All Fields] OR "cT1b"[All Fields] AND "ablation"[All Fields] OR "radiofrequency ablation"[All Fields] OR "radiofrequency ablation"[MeSH Terms] OR "catheter ablation"[MeSH Terms] OR "catheter ablation"[MeSH Terms] OR "catheter ablation"[MeSH Terms] Journal Article, English (2000-2020).
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