

Supplementary file (Part 1 paper)

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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	%	$\Delta -\geq 4$	$\Delta -\geq 2$	$\Delta -\geq 1$	=	$\Delta +\geq 1$	$\Delta +\geq 2$	$\Delta +\geq 4$
90-day grade ≥ 3 morbidity/toxicity	%	$\Delta -\geq 20$	$\Delta -\geq 10$	$\Delta -\geq 5$	=	$\Delta +\geq 5$	$\Delta +\geq 10$	$\Delta +\geq 20$
QOL (all domains)	Norm scale	$\Delta -\geq 20$	$\Delta -\geq 10$	$\Delta -\geq 5$	=	$\Delta +\geq 5$	$\Delta +\geq 10$	$\Delta +\geq 20$
FEV1% (pre vs. post), healthy patient	Absol FEV1%	$\Delta -\geq 40$	$\Delta -\geq 20$	$\Delta -\geq 10$	=	$\Delta +\geq 10$	$\Delta +\geq 20$	$\Delta +\geq 40$
FEV1% (pre vs. post), severe COPD	Absol FEV1%	$\Delta -\geq 20$	$\Delta -\geq 10$	$\Delta -\geq 5$	=	$\Delta +\geq 5$	$\Delta +\geq 10$	$\Delta +\geq 20$
5-year OS	%	$\Delta -\geq 20$	$\Delta -\geq 10$	$\Delta -\geq 5$	=	$\Delta +\geq 5$	$\Delta +\geq 10$	$\Delta +\geq 20$
5-year LCSS	%	$\Delta -\geq 20$	$\Delta -\geq 10$	$\Delta -\geq 5$	=	$\Delta +\geq 5$	$\Delta +\geq 10$	$\Delta +\geq 20$
FFR	% ^a	$\Delta -\geq 20$	$\Delta -\geq 10$	$\Delta -\geq 5$	=	$\Delta +\geq 5$	$\Delta +\geq 10$	$\Delta +\geq 20$
LR FFR	% ^a	$\Delta -\geq 20$	$\Delta -\geq 10$	$\Delta -\geq 5$	=	$\Delta +\geq 5$	$\Delta +\geq 10$	$\Delta +\geq 20$

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

^a, actuarial % at ≥ 2 years, if not available crude incidence.

Absol, absolute difference in % predicted value; COPD, chronic obstructive pulmonary disease; FFR, freedom from recurrence; LCSS, lung cancer specific survival; LR, loco-regional; Norm scale; normalized scale (0–100); pre vs. post, pre-treatment vs. ≥ 6 months later; QOL, quality of life; OS, overall survival.

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 $\geq 80\%$ is regarded as normal, that dyspnea on exertion is rarely noted for FEV1 $\geq 60\%$, 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).

Generally Healthy Patients, cI (8th Ed) NSCLC

SBRT / ABL v Open Surgery

Intermediate (1-2 year) Outcomes

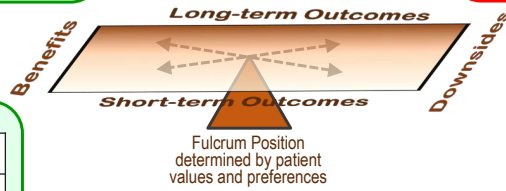
	SBRT (v Lobe) Effect: Conf	SBRT (v SL) Effect: Conf	ABL (v SL) Effect: Conf	ABL (v SBRT) Effect: Conf
Δ FEV1	↑↑ +	= 0	- -	- -
Dyspnea	↑ +	= 0	- -	- -
QOL	↑↑ +	↑↑ 0	↑↑ 0	= 0
Pain	↑↑ +	↑↑ 0	↑↑ 0	- -

Long-Term (5-year) Outcomes

	SBRT (v Lobe) Effect: Conf	SBRT (v SL) Effect: Conf	ABL (v SL) Effect: Conf	ABL (v SBRT) Effect: Conf
OS	↓↓↓ +++	↓↓↓ +++	↓↓↓ +	↓ +
LCSS	↓↓↓ +	↓↓↓ +	↓↓↓ +	- -
FFR	↓↓ +	- -	- -	- -
LR-FFR	↓ +	- -	- -	- -

Short-Term (90-day) Outcomes

	SBRT v Lobe/SL Effect: Conf	ABL (v SL) Effect: Conf	ABL (v SBRT) Effect: Conf
Mortality	↑↑ +++	= / ↑ 0	↓ 0
Morbidity	↑ +	= / ↑ 0	↓ 0
QOL	↑↑ +	- -	- -
Pain	↑↑ +	↑↑ Extpol	- -



Legend

Effect	Confidence in / Consistency of Data
↑↑↑	2x meaningful improvement
↑↑	Meaningful improvement
↑	Somewhat better
=	Similar
↓	Somewhat worse
↓↓	Meaningful worsening
↓↓↓	2x meaningful worsening
++++	Very High
+++	High
++	Moderate
+	Low
0	Very Low
Extpol	Extrapolation

Nuances
 No difference between peripheral and central tumors, but toxicity over time with SBRT for ultra-central tumors is a concern
 Tumor size does not affect relative differences

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.

Older Patients, cI (8th Ed) NSCLC

**SBRT / ABL v
Open Surgery**

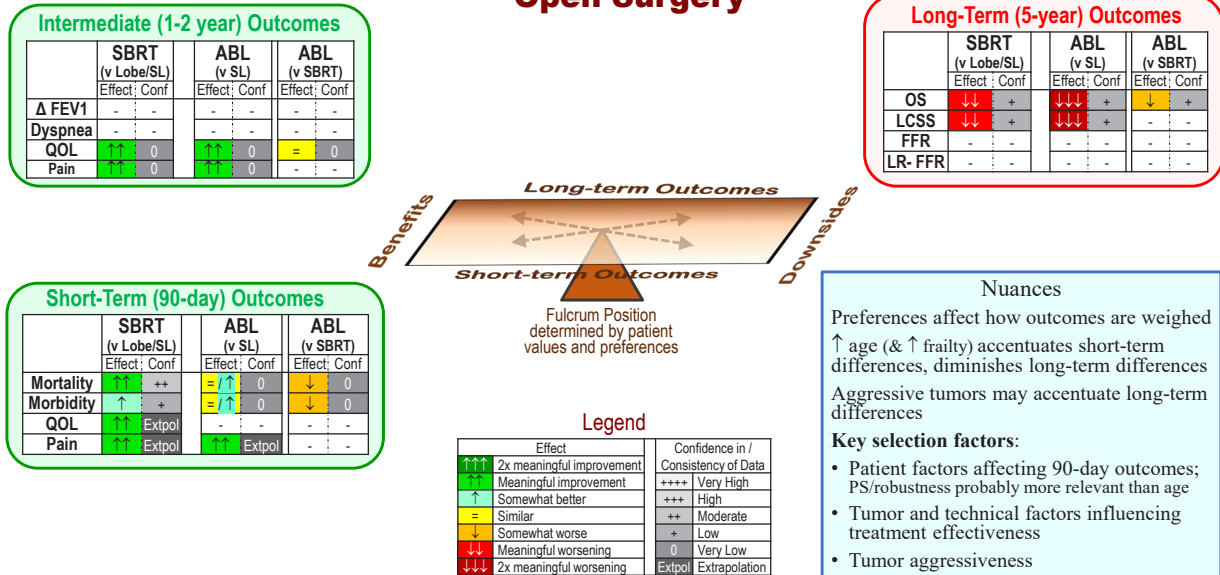


Figure S1-2 Decision guide for older patients—SBRT/ablation *vs.* open surgery.

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.

Compromised Patients, cI (8th Ed) NSCLC

SBRT / ABL v Open Surgery

Intermediate (1-2 year) Outcomes

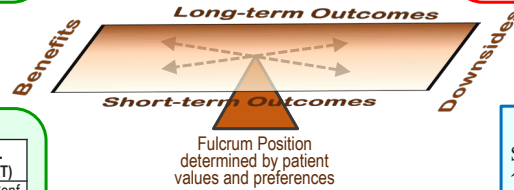
	SBRT (v Lobe/SL)		ABL (v SL)		ABL (v SBRT)	
	Effect	Conf	Effect	Conf	Effect	Conf
Δ FEV1	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	-
QOL	↑↑↑	Extpol	↑↑↑	Extpol	=	Extpol
Pain	↑↑↑	Extpol	↑↑↑	Extpol	-	-

Long-Term (5-year) Outcomes

	SBRT (v Lobe)		SBRT (v SL)		ABL (v SL)		ABL (v SBRT)	
	Effect	Conf	Effect	Conf	Effect	Conf	Effect	Conf
OS	↓	+	↓	+	↓↓↓	0	↓	0
LCSS	↓	+	↓	+	↓↓↓	0	-	-
FFR	-	-	-	-	-	-	-	-
LR-FFR	-	-	-	-	-	-	-	-

Short-Term (90-day) Outcomes

	SBRT (v Lobe/SL)		ABL (v SL)		ABL (v SBRT)	
	Effect	Conf	Effect	Conf	Effect	Conf
Mortality	↑↑↑	Extpol	= / ↑	0	↓	0
Morbidity	↑↑↑	Extpol	= / ↑	0	↓	0
QOL	↑↑↑	Extpol	-	-	-	-
Pain	↑↑↑	Extpol	↑↑↑	Extpol	-	-



Legend

Effect	Confidence in / Consistency of Data
↑↑↑↑	2x meaningful improvement
↑↑↑	Meaningful improvement
↑	Somewhat better
=	Similar
↓	Somewhat worse
↓↓	Meaningful worsening
↓↓↓	2x meaningful worsening
+	Very High
+++	High
++	Moderate
+	Low
0	Very Low
Extpol	Extrapolation

Nuances

Strong impact of patient preferences/values
 ↑ compromise appears to proportionally ↑ morbidity/toxicity of all modalities

Selection is crucial (but undefined)
 Proposed process:

1. Assess risk and impact of acute toxicity for each modality (specific treatment- & patient-related risks, patient resilience)
2. Assess risk of delayed toxicity
3. Assess impact of long-term outcome differences

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
<i>1. What are the short-term outcomes in patients with cIA NSCLC undergoing lobectomy compared to either segmentectomy or wedge resection?</i>		
Population	Patients with cIA ^a NSCLC (treatment naïve)	Not NSCLC, not cIA ^a , 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
<i>2. What are the long-term outcomes in patients with cIA NSCLC undergoing lobectomy compared to either segmentectomy or wedge resection?</i>		
Population	Patients with cIA ^a NSCLC (treatment naïve)	Not NSCLC, not cIA ^a , 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
<i>3. What are the short-term outcomes in patients with cIA NSCLC undergoing SBRT compared to surgical resection (lobectomy, segmentectomy or wedge resection)?</i>		
Population	Patients with cIA ^a NSCLC (treatment naïve)	Not NSCLC, not cIA ^a , 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
<i>4. What are the long-term outcomes in patients with cIA NSCLC undergoing SBRT compared to surgical resection (lobectomy, segmentectomy or wedge resection)?</i>		
Population	Patients with cIA ^a NSCLC (treatment naïve)	Not NSCLC, not cIA ^a , 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 ^a NSCLC (treatment naïve)	Not NSCLC, not cIA ^a , 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 ^a NSCLC (treatment naïve)	Not NSCLC, not cIA ^a , 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 ^a NSCLC (treatment naïve)	Not NSCLC, not cIA ^a , 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 ^a NSCLC (treatment naïve)	Not NSCLC, not cIA ^a , 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

^a, 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:

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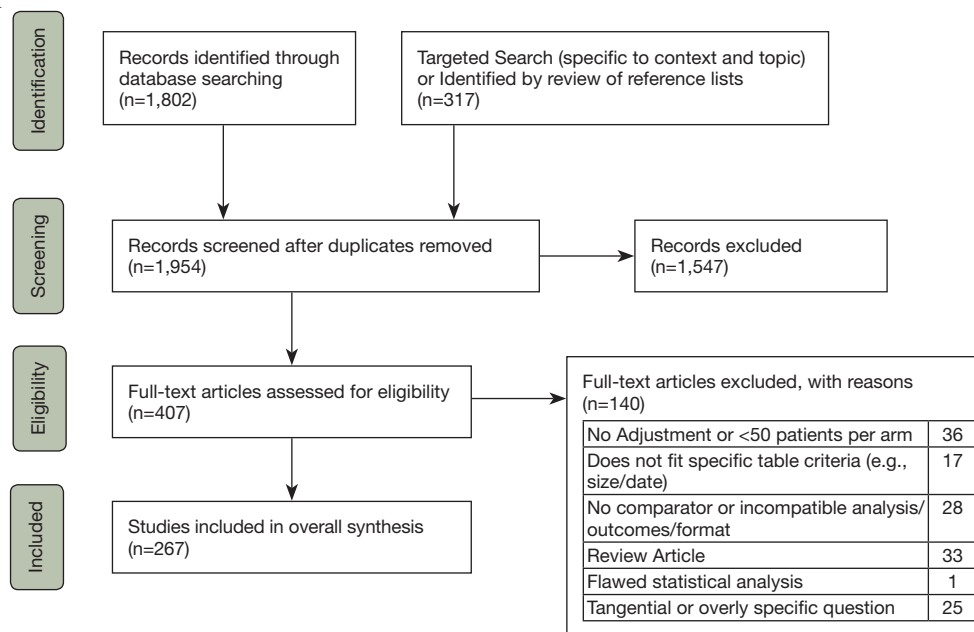
JCOG 1211 Kenji Suzuki, Japan 2-24-2020

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.

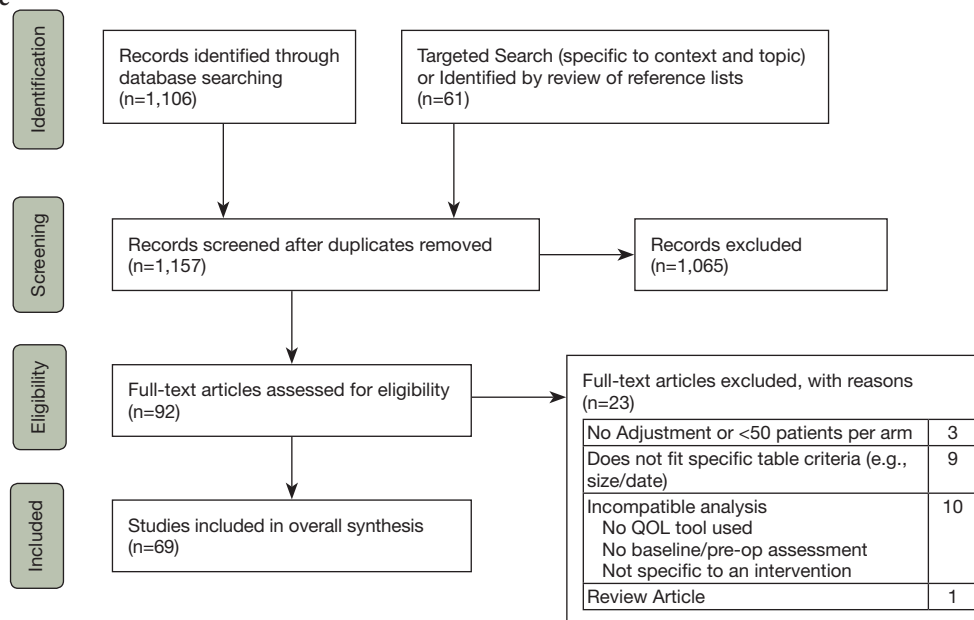
Resection extent



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 "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" OR "stage1" 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]).

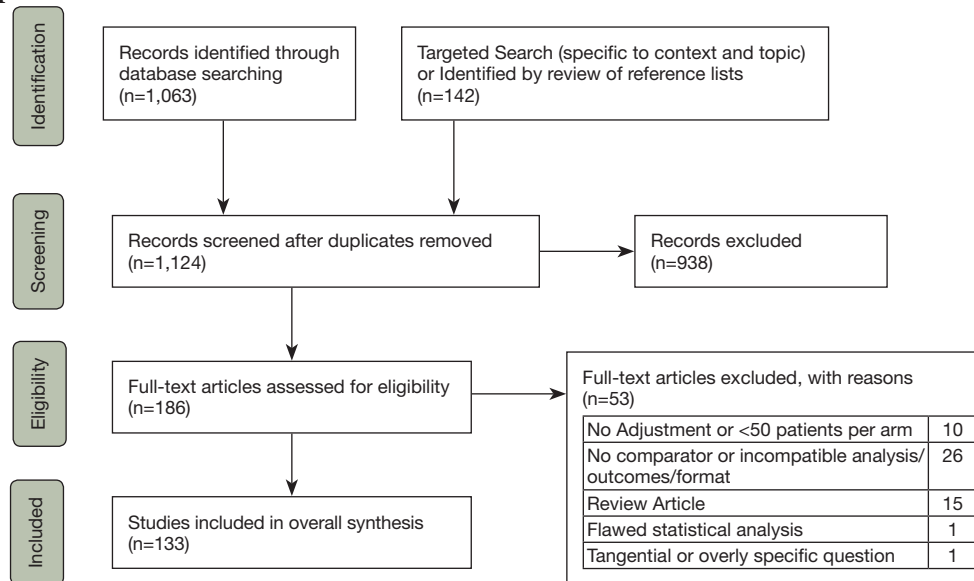
Quality of life



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 "carcinoma 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 ("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])).

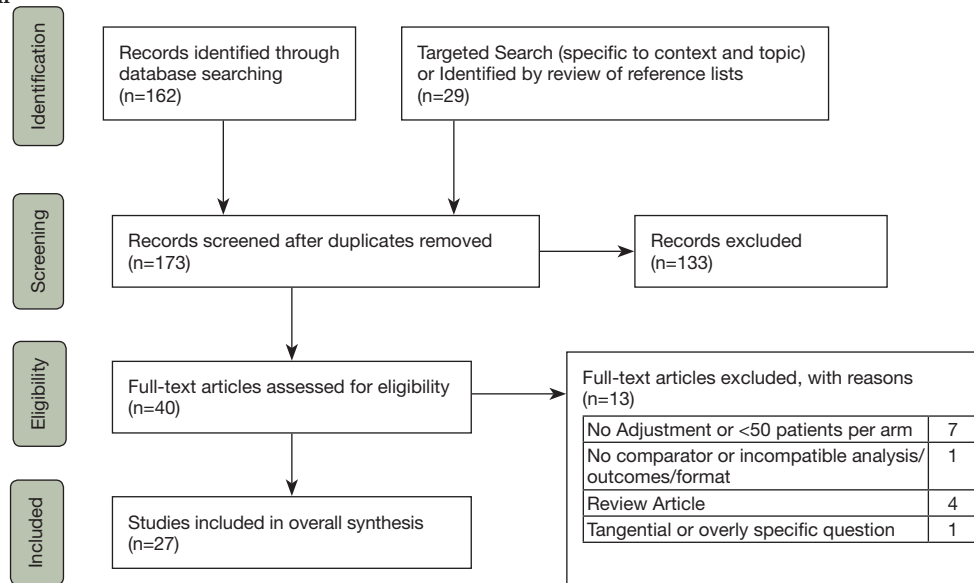
SBRT



Search string: SBRT review:

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Ablation



Search string: ablation review:

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References

1. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol* 2014;32:1277-80.
2. Wyrwich KW, Fihn SD, Tierney WM, et al. Clinically important changes in health-related quality of life for patients with chronic obstructive pulmonary disease: an expert consensus panel report. *J Gen Intern Med* 2003;18:196-202.
3. Wyrwich KW, Metz SM, Kroenke K, et al. Measuring patient and clinician perspectives to evaluate change in health-related quality of life among patients with chronic obstructive pulmonary disease. *J Gen Intern Med* 2007;22:161-70.
4. Maringwa JT, Quinten C, King M, et al. Minimal important differences for interpreting health-related quality of life scores from the EORTC QLQ-C30 in lung cancer patients participating in randomized controlled trials. *Support Care Cancer* 2011;19:1753-60.
5. Ilonen IK, Räsänen JV, Knuutila A, et al. Quality of life following lobectomy or bilobectomy for non-small cell lung cancer, a two-year prospective follow-up study. *Lung Cancer* 2010;70:347-51.
6. Yost KJ, Eton DT, Garcia SE, et al. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. *J Clin Epidemiol* 2011;64:507-16.
7. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16:139-44.
8. Sloan JA. Assessing the minimally clinically significant difference: scientific considerations, challenges and solutions. *COPD* 2005;2:57-62.