


# BMJ Open Surgical resection, radiotherapy and percutaneous thermal ablation for treatment of stage 1 non-small cell lung cancer: protocol for a systematic review and network meta-analysis

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## ABSTRACT

**Introduction** Non-small cell lung cancer (NSCLC) makes up the majority of lung cancer cases. Currently, surgical resection is the gold standard of treatment. However, as patients are becoming medically more complex presenting with advanced disease, minimally invasive image-guided percutaneous ablations are gaining popularity. Therefore, comparison of surgical, ablative and second-line external beam therapies will help clinicians, as management of NSCLC changes. We will conduct a meta-analysis, reviewing literature investigating these therapies in adult patients diagnosed with stage 1 NSCLC, with neither hilar nor mediastinal nodal involvement, confirmed either through cytology or histology regardless of type.

**Methods and analysis** We will search electronic databases (MEDLINE, Embase, Web of Science, Scopus, ClinicalTrials.gov, Cochrane) from their inception to January 2021 to identify randomised controlled trials (RCTs), cluster RCTs and cohort studies comparing survival and clinical outcomes between any two interventions (lobectomy, wedge resection, video-assisted thoracoscopic surgery/robot-assisted thoracoscopic surgery, radiofrequency ablation, microwave ablation, cryoablation and consolidated radiation therapies (external beam radiation therapy, stereotactic body radiation therapy, and 3D conformal radiation therapy). The primary outcomes will include cancer-specific survival, lung disease-free survival, locoregional recurrence, death, toxicity and non-target organ injury. We will also search published and unpublished studies in trial registries and will review references of included studies for possible inclusion. Risk of bias will be assessed using tools developed by the Cochrane collaboration. Two reviewers will independently assess the eligibility of studies and conduct the corresponding risk of bias assessments. For each outcome, given enough studies, we will conduct a network meta-analysis. Finally, we will use the Confidence in Network Meta-Analysis tool to assess quality of the evidence for each of the primary outcomes.

**Ethics and dissemination** We aim to share our findings through high-impact peer review. As interventional

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ We can use this meta-analysis as a basis to compare surgical, external beam and percutaneous image-guided therapies, aiding in selecting therapeutic strategy for non-surgical candidates.
- ⇒ This study will serve as a foundation for future trials to compare these treatment options within one study population.
- ⇒ Interventions in this study are characterised into categories (lobectomy, wedge resection, video-assisted thoracoscopic surgery/robot-assisted thoracoscopic surgery, radiofrequency ablation, microwave ablation, cryoablation and radiation therapy), meaning we will likely not be able to account for variations of a given treatment within or between studies.

techniques become more popular, it will be important for providers in multidisciplinary teams caring for these patients to receive continuing medical education related to these interventions. Data will be made available to readers. **PROSPERO registration number** CRD42021276629.

## BACKGROUND

### Description of the condition

Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases and is a leading cause of cancer mortality worldwide. NSCLC is a heterogeneous set of epithelial lung malignancies consisting of three major subtypes: adenocarcinoma (ADC), squamous cell carcinoma (SCC) and large cell carcinoma (LCC). These subtypes together account for a 5-year survival rate of about 25%.<sup>1</sup>

One factor that contributes to the poor survival is the non-specific, late-appearing symptoms at presentation which cause delays in diagnosis. Approximately 75% of NSCLC

cases present with inoperable locally advanced or metastatic disease, with a dismal 5-year survival rate of less than 5%.<sup>2</sup>

Adoption of high-resolution low-dose CT (LDCT) screening with the intent of early detection in high-risk individuals has led to increased identification of smaller, early-stage NSCLC more amenable to curative intervention, with a correspondingly higher 5-year survival rate of 50%–70% following resection. The advent of LDCT screening following the updated 2013 US Preventive Services Task Force recommendations has also resulted in a stage shift with increased incidence of stage 1 lung cancer cases from 19% to 27%.<sup>3</sup> The success in LDCT lung cancer screening has resulted in identification of a larger population of potentially curable stage 1 NSCLC. Surgical intervention (lobectomy, wedge resection) remains the gold standard for treatment of early-stage, resectable NSCLC. However, only 15%–30% of patients are potential surgical candidates due to limited cardiopulmonary reserve, advanced age and other disqualifying comorbidities.<sup>4</sup> This has led to an increased use of minimally invasive therapeutic options for high-risk patients with stage 1 NSCLC, including both radiation therapies (RT) and image-guided percutaneous ablation.

## Description of the intervention

### Surgical approaches

Surgical resection has been the standard of care for early-stage NSCLC since the 1995 Lung Cancer Study Group (LCSG) trial.<sup>5</sup> Surgical treatment in the form of lobectomy, or more limited sublobar resections (segmentectomy, wedge resection), involves the excision of lung parenchyma that is involved with tumour, leaving an appropriate margin of normal tissue. Anatomical resections, including lobectomy and segmentectomy, differ from wedge resection due to concurrent removal of interlobar and parenchymal (N1) lymph nodes for more accurate pathological staging.<sup>6</sup> For patients with adequate physiological reserve, lobectomy is preferred over wedge resection due to lower rates of locoregional recurrence.<sup>5</sup> Recently, video-assisted thoracoscopic surgery (VATS) and robot-assisted thoracoscopic surgery (RATS) have been employed to perform lobectomies and segmentectomies in patients with NSCLC with strong evidence.<sup>7</sup> More recent studies since the 1995 LCSG trial have indicated equivalency in long-term survival for stage 1 lung cancers.<sup>8,9</sup>

For the significant subset of older patients with NSCLC with limited cardiopulmonary reserve who cannot tolerate surgery, a variety of non-surgical interventions including external beam therapies including stereotactic body radiation therapy (SBRT) or proton therapy, and percutaneous thermal ablative therapies such as radiofrequency, microwave or cryoablation have emerged as viable alternatives to surgical resection.

### External beam therapies

#### Stereotactic body radiation therapy

SBRT, also referred to as stereotactic ablative radiotherapy, is a form of precision RT that delivers high

doses of radiation to an image-defined mass. SBRT uses multiple beam angles to achieve sharp dose gradients that conform to the tumour with a minimal margin of surrounding normal tissue. SBRT also makes use of respiratory gating as well as patient immobilisation systems to account for tumour motion during treatment delivery, allowing high-dose radiation to be delivered to tumour in a reproducible manner.<sup>10</sup> Conventional RT for early-stage inoperable NSCLC has typically consisted of radiotherapy fractionated to a total dose of 60 Gy given over multiple fractions over several weeks.<sup>11</sup> In contrast, SBRT uses a hypofractionated regimen of five or fewer fractions of 10–20 Gy each to deliver the same total dose over a much shorter treatment period, reducing potential damage to surrounding tissue. In recent years, SBRT has emerged as the primary alternative therapy for early-stage NSCLC to surgical resection, with an increase in utilisation from 6.7% to 16.3% from 2008 to 2013, while the rate of lobectomy/pneumonectomy has declined from 49.5% to 43.7% over the same period.<sup>12</sup>

#### Proton therapy

Proton beam therapy (PBT) is an evolving modality within radiotherapy involved with numerous cancer types; however, its role in treatment of NSCLC is still not fully understood. As many as 25% of patients experience isolated locoregional recurrence and toxicity with standard radiation techniques.<sup>13</sup> PBT allows for sharp dose build-up and drop-off, reducing local exposure of radiation to uninvolved organs (ie, heart, spinal cord, oesophagus and healthy lung parenchyma). In addition, protons have a higher biological effectiveness compared with photons,<sup>14</sup> and as patients with NSCLC live longer this becomes important to long-term management of this disease. It is speculated that protons may spare circulating lymphocytes from radiation by reducing the volume of blood that is radiated, preventing lymphopenia which has been correlated to worse outcomes.<sup>15</sup> However, proton therapy has been linked with increased chest wall pain and dermatitis, likely due to beam entry or end ranging into thoracic chest wall anatomy.<sup>14</sup> There is one randomised trial comparing protons to photons in early-stage NSCLC<sup>16</sup> which closed early due to concerns about lack of volumetric image-guided RT and poor accrual likely due to lack of insurance coverage. Comparison of this new form of radiotherapy to gold standard surgery and emerging interventional techniques would help assess efficacy and aid further investigation.

#### Percutaneous thermal ablative therapies

Using CT guidance, probes can be percutaneously inserted through the chest wall, and once an adequate ablative radius is imaged, the ablative therapy of choice (ie, radiofrequency, microwave and cryoablation) can be administered.

### Radiofrequency ablation

Radiofrequency ablation (RFA) involves the delivery of a high-frequency electrical alternating current (approximately 375–480 kHz) leading to ion movement producing heat and protein denaturation. Temperatures up to 95°C can be reached in about 15 min; however, efficacy can be limited by the heatsink phenomenon from nearby vessels and airways that can shunt heat away to subtherapeutic levels. Unlike microwave and cryoablation, RFA uses a single active probe at a time due to potential for electrical interference between probes.

### Microwave ablation

Microwave ablation (MWA) stimulates water molecules in tissue to create heat, which leads to immediate protein denaturation. Theoretically, MWA can generate higher temperatures in a larger volume in a shorter time than RFA, although results between these ablative therapies are comparable. MWA is favourable in ablation adjacent to large vessels and airways due to lower sensitivity to the heatsink phenomenon.

### Cryoablation

Cryoablation uses pressurised argon and helium to freeze tissue in contact with the ablation probes. Multiple freezing cycles are required as air in normal lung parenchyma limits the size of the ice ball that forms. On thawing, intra-alveolar haemorrhage displaces the air, allowing for larger ice balls to form, increasing necrosis zone size. Freezing and thawing cycles induce protein denaturation, membrane rupture and ischaemia within the zone of ablation. Complications of percutaneous ablative therapies include pneumothorax, haemorrhage and local probe site infections, which were rare.<sup>17 18</sup>

### Why it is important to do this review

The ability of LDCT lung cancer screening to detect an ever-increasing number of patients with stage 1 NSCLC amenable to curative therapy warrants a re-examination of the current therapeutic options available to this population. Though the efficacy of surgical resection of local disease in these patients has long been demonstrated, a majority of patients (70%) are unable to tolerate surgery, thus requiring alternative treatment options. In this systematic review and network meta-analysis (NMA), we will evaluate the variety of non-surgical interventions that have evolved to treat stage 1 NSCLC, including RTs and percutaneous ablative therapies.

## METHODS AND ANALYSIS

This protocol has followed the reporting guidelines of, and is in compliance with, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols (online supplemental material).<sup>19</sup> Any changes to this protocol will be delineated in the final article and will be reflected in an updated version of the PROSPERO

registration. The methods section of this protocol is based on previously published protocols.<sup>20–22</sup>

### Patient and public involvement

No patients nor any members of the public were involved in the development of this protocol, nor will they be included in the completion or dissemination of the corresponding review and results.

### Criteria for considering studies for this review

#### Types of studies

In the review, we will include all randomised controlled trials (RCTs), cluster RCTs and cohort studies comparing any two interventions (see below) against one another or against a placebo. We will not exclude studies on the basis of language, date of publication or setting.

#### Types of participants

We will include adult patients diagnosed with stage 1 NSCLC<sup>23</sup> with neither hilar nor mediastinal nodal involvement. We will include patients whose status was confirmed either through cytology or histology of samples obtained at the time of intervention without regard to the type of NSCLC (ie, ADC, SCC or LCC).

#### Types of interventions

We plan to compare eight excisional therapies, ablation therapies and RTs. The excisional treatments are (1) lobectomy, (2) wedge resection, (3) segmental resection, and (4) VATS/RATS. The ablation techniques are (1) RFA, (2) MWA, and (3) cryoablation. RTs including external beam radiation therapy (EBRT), SBRT and 3D conformal radiation therapy (3D-CRT) will be consolidated for ease of comparison. Given that this may induce some degree of heterogeneity, should we have sufficient studies, we will conduct our analysis with the more granular categorisations. Studies will be included if they compare any combination of interventions to one another or against no treatment or placebo. Should the specific treatment not be specified, we will explore broader definitions of the interventions. As we are interested in the modality of the interventions, we will not define interventions in terms of the pharmacotherapeutic agents (where applicable); this will be explored as a subgroup analysis if possible.

#### Types of outcome measures

##### Primary outcomes

- ▶ Cancer-specific survival (CSS).
- ▶ Lung disease-free survival (DFS).
- ▶ Locoregional recurrence.
- ▶ Death.
- ▶ Toxicity.
- ▶ Non-target organ injury.

##### Secondary outcomes

###### Major

- ▶ CSS.
- ▶ DFS.
- ▶ Lung DFS.



- ▶ Residual disease.
- ▶ Locoregional recurrence.
- ▶ Toxicity.
- ▶ Quality-adjusted life-years.
- ▶ Infection.
- ▶ Haemoptysis.
- ▶ Bleeding.
- ▶ Haemothorax.
- ▶ Pneumothorax.

#### Minor

- ▶ Fever.
- ▶ Nausea.
- ▶ Vomiting.
- ▶ Shortness of breath.
- ▶ Chest pain.

#### Search methods for identification of studies

We will conduct a systematic literature search to identify all published and unpublished trials for possible inclusion in this review. We will adapt the search strategy we developed for MEDLINE via PubMed (online supplemental appendix 1) to search five electronic databases.

We will conduct searches in the following databases (from their inception to present):

- ▶ Embase (embase.com): 1947 to present (online supplemental appendix 2).
- ▶ Web of Science Classic Core Collections: 1900 to present (online supplemental appendix 3). Includes: Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index, Conference Proceedings Citation Index–Science, Conference Proceedings Citation Index–Social Sciences & Humanities, Book Citation Index–Science, Book Citation Index–Social Sciences & Humanities, Emerging Sources Citation Index, Current Chemical Reactions, Index Chemicus.
- ▶ Scopus (scopus.com): 1788 to present (online supplemental appendix 4).
- ▶ Cochrane (cochrane.org): 1996 to present (online supplemental appendix 5).
- ▶ ClinicalTrials.gov: 2008 to present (online supplemental appendix 6).

We will apply no restriction on language of publications. We will also conduct a search of unpublished and ongoing trials in ClinicalTrials.gov (www.clinicaltrials.gov) (online supplemental material). In addition, we will screen the references of all included studies.

#### Data collection

##### Selection of studies

All references from the search strategy (see above) will be imported into Covidence.<sup>24</sup> Two authors will independently screen abstracts and titles for possible inclusion in the review. The full text of the potentially included studies will be obtained, by which two authors will conduct a full-text assessment against the inclusion and exclusion criteria delineated above for inclusion in the review,

noting the reason for exclusion where applicable. At each stage, disagreement will be resolved through discussion, and where this is not possible, a third author will make a final decision. The final set of inclusions and exclusions will be depicted in a PRISMA flow chart (online supplemental appendix 7).<sup>25</sup>

#### Data extraction and management

Two reviewers will independently extract the data from each of the included studies using a standardised extraction form (items enumerated below). As in the critical appraisal, any disagreements will be resolved through discussion or by a third reviewer if necessary. Relevant extracted data will be entered into Review Manager V.5<sup>26</sup> by one author and checked for accuracy by a second author. Data will then be exported to R.<sup>27</sup>

From each study, insofar as the information is available, we will extract information on study characteristics, outcomes and potential effect modifiers. If information is missing or additional information is needed (eg, for risk of bias assessment), the corresponding authors of the study will be contacted.

#### Study characteristics data

We will extract the article title, name of corresponding author, date of publication, type of publication, study setting, sources of funding, all conflicts of interest, study design, patient characteristics (eg, age and gender), time of histological confirmation (eg, through biopsy prior to intervention or at the time of intervention) and study-level inclusion/exclusion criteria (eg, tumour size).

#### Outcome data

We will extract the interventions being compared and all primary and secondary outcome measures (and corresponding measure of uncertainty). In RCTs, we will aim to extract arm-level data or, where this is not possible, study-level data. For observational studies, we will extract adjusted effect estimates or, if unavailable, unadjusted effect estimates—each with corresponding measure of uncertainty.

#### Potential effect modifier data

Additionally, we will extract trial size, rates of attrition. Moreover, if defined as an inclusion/exclusion criterion for a given study, we will extract the type of tumour, lung parity, node on which the tumour was found and method of ascertainment for outcomes (only those corresponding to this review).

#### Risk of bias

Results of the meta-analyses will be contextualised by the risk of bias from included studies. Two reviewers will independently assess the risk of bias of qualifying studies and as above, any disagreement will be resolved through discussion or, if necessary, with a third reviewer.

The risk of bias in RCTs will be evaluated using the Cochrane Risk of Bias (RoB)<sup>28 29</sup> tool against the following domains:

- ▶ Bias arising from the randomisation process.
- ▶ Bias due to deviations from intended interventions.
- ▶ Bias due to missing outcome data.
- ▶ Bias in measurement of the outcome.
- ▶ Bias in the selection of the reported result.

Based on signalling questions corresponding to each domain ('Yes', 'Potentially Yes', 'Potentially No', 'No' or 'No Information'), the risk of bias in each domain as well as the overall risk of bias will be ranked as 'low risk of bias', 'unclear risk of bias' or 'high risk of bias'. Should quasi-RCTs be included in the review, their corresponding risk of bias will be assessed using an additional domain as discussed in the *Cochrane Handbook for Systematic Reviews of Interventions*.<sup>29</sup>

Non-randomised studies (NRS) will be evaluated using the Cochrane Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool—a tool that seeks to evaluate the risk of bias of an NRS as through the NRS were emulating an RCT (ie, a target trial).<sup>30</sup> The risk of bias will be evaluated across seven domains:

- ▶ Bias due to confounding.
- ▶ Bias in selection of participants into the study.
- ▶ Bias in classification of interventions.
- ▶ Bias due to deviations from intended interventions.
- ▶ Bias due to missing data.
- ▶ Bias in measurement of the outcome.
- ▶ Bias in selection of the reported result.

As in the case of the RoB tool, the bias for each domain, in addition to the overall risk of bias, will be assessed by series signalling questions (ie, 'Yes', 'Potentially Yes', 'Potentially No', 'No' or 'No Information'), yielding domain and overall risk of bias assessments of 'low', 'moderate', 'serious' or 'critical'.

## Data synthesis

### Characteristics of included studies

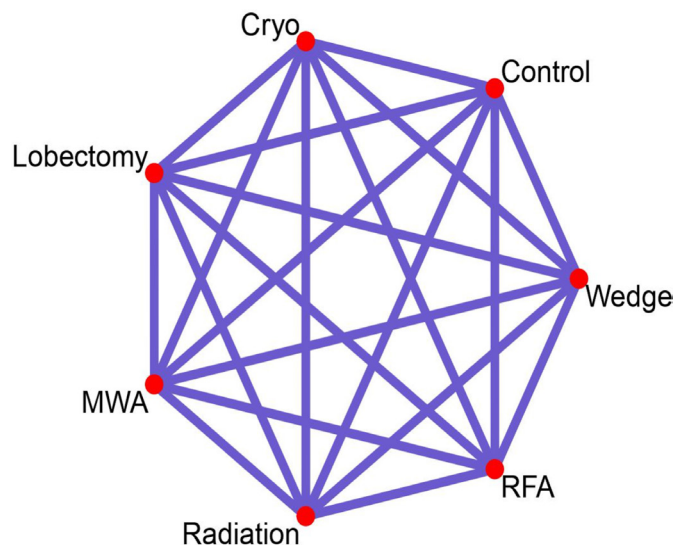
All included studies will be summarised through descriptive statistics. We will report on study population characteristics, including types of comparisons, design characteristics. For each outcome, we will present a network diagram, with nodes proportional to the number of patients, and edges proportional to the number of studies per comparison (figure 1).

### Relative treatment effect

Pairwise relative treatment effects will be estimated using the OR for dichotomous outcomes, mean difference or standardised mean difference for continuous outcomes and HRs for time-to-event or survival outcomes. For each outcome, we will report on the overall ranking of treatments obtained by the surface under the cumulative ranking curve or p score providing a scalar value from 0 (least effective) to 1 (most effective) of each treatment for a given outcome.<sup>31</sup>

### Pairwise meta-analysis

For each pairwise comparison, if more than one study is present, we will conduct a pairwise meta-analysis using



**Figure 1** The network structure of possible comparisons between Lobectomy, wedge resection (Wedge), radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation (Cryo), Radiation and Control (eg, no treatment). Red dots denote interventions and edges denote comparisons.

an inverse variance-weighted random-effects model. Estimation will be achieved using the restricted maximum likelihood estimator. Between-study heterogeneity will be estimated using the  $I^2$  statistic and corresponding 95% CI.<sup>32</sup> Analyses will be carried out in R<sup>27</sup> using the *meta* package.<sup>33</sup> Given the possibility of small trials, we will estimate the summary effect estimates using the Hartung-Knapp-Sidik-Jonkman method.<sup>34 35</sup>

### Network meta-analysis

Given the likely clinical and methodological heterogeneity, we will fit a random-effects NMA model for each outcome (data permitting) and will account for the correlation from multiarm trials. Common between-study variance will be assumed. Given that we will include both RCTs and NRS in the review, for each outcome, we will (1) fit a network to RCTs only, (2) fit a network to NRS only, (3) fit a network to all studies (RCT and NRS), (4) fit a 'design-adjusted' NMA, and (5) fit a 'three-level hierarchical' NMA.<sup>20</sup>

### Assessment of heterogeneity

#### Clinical and methodological heterogeneity

For pairwise meta-analyses, we will explore the heterogeneity by visual inspection of forest plots and estimated using the  $I^2$  statistic with corresponding 95% CI.<sup>32 36</sup> Additionally, we will pay attention to meaningful clinical groupings that may account for heterogeneity.

#### Assessment of transitivity

A key assumption in NMA is that effect modifiers do not differ in their distributions across treatment comparisons. Thus, we will compare the distribution of the potential effect modifiers across each pairwise comparison using the direct evidence.



### Assessment of statistical inconsistency

To assess local inconsistency, we will use the back-calculation method.<sup>37</sup> In addition, we will use the design-by-treatment interaction model to assess global inconsistency.<sup>38</sup> Tests of consistency will be conducted in R using the *netmeta* package<sup>39</sup>. For networks with randomised studies and NRS, we will assess differences between the types of evidence (direct randomised, direct non-randomised, indirect randomised and indirect non-randomised) as described in ref 20. Data permitting, discrepancies between the types of evidence will be further investigated, and if a source of disagreement is identified, where possible, we will conduct network meta-regression.<sup>40</sup>

### Unit of analysis issues and missing data

Multicentre trials will be included and the correlation between effect estimates will be accounted for in the network. We do not anticipate any cluster or cross-over RCTs. Should any such studies be included, however, we will proceed under the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions*.<sup>29</sup> All analyses will be carried out on an intention-to-treat basis. For each included study, we will investigate the extent of missing data and evaluate the methods by which this was addressed in the risk of bias evaluation. For primary outcomes, we will conduct a sensitivity analysis to evaluate the impact of including studies for which there is a meaningful degree of missing data. Throughout, where possible, measures of uncertainty will be transformed to SEs. Should no certainty be given or inferred, we will take the mean of known SEs from the included studies.<sup>41 42</sup>

### Assessment of reporting biases

To assess the possibility of reporting bias and small-study effects, we will visually inspect the funnel plots<sup>43</sup> or each treatment where possible (ie, at least 10 studies for a given treatment). Additionally, to evaluate small-study effects, we will assess comparison-adjusted funnel plots<sup>44</sup> and, where possible, conduct meta-regression with study variance as the covariate.<sup>45 46</sup>

### Exploring heterogeneity and inconsistency

For the primary outcomes, we will explore the following sources of possible heterogeneity: cancer type, lung parity, lobe on which node is found, tumour size and method of ascertainment for outcomes. Should sufficient studies be available, we will conduct subgroup analyses based on the characteristics. In addition, for the primary outcomes, we will endeavour to perform sensitivity analyses for:

- ▶ Study size (ie, restricting to larger studies as smaller studies may lead to publication bias). Study size will be determined by the median of included studies, such that in the sensitivity analysis, we will exclude studies whose size is below the median.
- ▶ Removal of studies with more than 20% missing data.

### Assessment of confidence in network estimates and summary of findings

The confidence of the network estimates for primary outcomes will be assessed using the Confidence in Network Meta-Analysis (CINeMA) framework.<sup>47 48</sup> For each of the primary outcomes, two authors will independently assess the six CINeMA domains: within study bias, across study bias, indirectness, imprecision, heterogeneity and incoherence<sup>47</sup> as very low, low, moderate, high confidence. This will be assessed using the online web tool.<sup>49</sup>

## CONCLUSIONS

### Limitations

The proposed study is not without limitations. Given that we are using aggregated data for our planned meta-analyses as opposed to an individual patient meta-analysis, we are only able to categorise our interventions into six categories: lobectomy, wedge resection, RFA, MWA, cryoablation and RT. This means, however, that we will likely not be able to account for variations of a given treatment within or between studies. Additionally, since we are likely to compare multiple interventions, it is possible that we find statistically significant results by chance alone; however, there are no well-established methods to account for this issue in systematic reviews. With these considerations in mind, we believe that while valuable, the corresponding results should be interpreted with caution.

### Summary

This systematic review and meta-analysis will serve as a foundation for comparison between the numerous treatment modalities and a tool for clinicians to help best tailor therapies for early-stage NSCLC. As medicine advances, patients are presenting with more comorbidities and may not be the best suited to receive surgery. Data assessing efficacy of interventional image-guided treatments compared with gold standard will be crucial for evidence-based decision-making in selecting therapeutic route and continuing innovation of these therapies.

### Ethics and dissemination

This study will not need new institution review board approval as this is a meta-analysis of previously published data. We aim to present our findings in high-impact peer-reviewed journals and conference presentations. As interventional techniques become more popular, it becomes important for all clinicians involved in the care of these patients to receive continuing medical education on this topic. Data synthesised in this study will be available to readers.

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## REFERENCES

- Lu T, Yang X, Huang Y, *et al.* Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. *Cancer Manag Res* 2019;11:943–53.
- Molina JR, Yang P, Cassivi SD, *et al.* Non-Small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc* 2008;83:584–94.
- Jonas DE, Reuland DS, Reddy SM, *et al.* Screening for lung cancer with low-dose computed tomography: updated evidence report and systematic review for the US preventive services Task force. *JAMA* 2021;325:971–87.
- Bhatia S, Pereira K, Mohan P, *et al.* Radiofrequency ablation in primary non-small cell lung cancer: what a radiologist needs to know. *Indian J Radiat Imaging* 2016;26:81–91.
- Ginsberg RJ, Rubinstein LV. *Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer.* Lung Cancer Study Group. *Ann Thorac Surg* 1995;60:615–23.
- Tandberg DJ, Kelsey CR, D'Amico TA, *et al.* Patterns of Failure After Surgery for Non-Small-cell Lung Cancer Invading the Chest Wall. *Clin Lung Cancer* 2017;18:e259–65.
- Hu X, Wang M. Efficacy and safety of robot-assisted thoracic surgery (rats) compare with video-assisted thoracoscopic surgery (VATS) for lung lobectomy in patients with non-small cell lung cancer. *Comb Chem High Throughput Screen* 2019;22:169–78.
- Landreneau RJ, Sugarbaker DJ, Mack MJ, *et al.* Wedge resection versus lobectomy for stage I (T1 N0 M0) non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 1997;113:691–700.
- Warwick R, Mediratta N, Shackcloth M, *et al.* Wedge resection versus lobectomy for stage 1 non-small-cell lung cancer. *Asian Cardiovasc Thorac Ann* 2013;21:566–73.
- Prunarety J, Boisselier P, Aillères N, *et al.* Tracking, gating, free-breathing, which technique to use for lung stereotactic treatments? A dosimetric comparison. *Rep Pract Oncol Radiother* 2019;24:97–104.
- Nyman J, Hallqvist A, Lund Jo-Åsmund, *et al.* SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol* 2016;121:1–8.
- Subramanian MP, Meyers BF. Surgical resection versus stereotactic body radiation therapy for stage I NSCLC: can randomized trials provide the solution? *Cancers* 2018;10. doi:10.3390/cancers10090310. [Epub ahead of print: 04 09 2018].
- Mesko S, Gomez D. Proton therapy in non-small cell lung cancer. *Curr Treat Options Oncol* 2018;19:76.
- Brooks ED, Ning MS, Verma V, *et al.* Proton therapy for non-small cell lung cancer: the road ahead. *Transl Lung Cancer Res* 2019;8:S202–12.
- Venkatesulu BP, Mallick S, Lin SH, *et al.* A systematic review of the influence of radiation-induced lymphopenia on survival outcomes in solid tumors. *Crit Rev Oncol Hematol* 2018;123:42–51.
- Nantavithya C, Gomez DR, Wei X, *et al.* Phase 2 study of stereotactic body radiation therapy and stereotactic body proton therapy for high-risk, medically inoperable, early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2018;101:558–63.
- Duka E, Ierardi AM, Floridi C, *et al.* The role of interventional oncology in the management of lung cancer. *Cardiovasc Intervent Radiol* 2017;40:153–65.
- Inoue M, Nakatsuka S, Jinzaki M. Cryoablation of early-stage primary lung cancer. *Biomed Res Int* 2014;2014:1–8.
- Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2016;354:i4086.
- Eftimiou O, Mavridis D, Debray TPA, *et al.* Combining randomized and non-randomized evidence in network meta-analysis. *Stat Med* 2017;36:1210–26.
- Venekamp RP, van Uum RT, Konstantinidis M. Non-Steroidal anti-inflammatory drugs (NSAIDs) for acute sore throat (protocol). *Cochrane Database of Systematic Reviews* 2020;8:CD013709.
- Hay S, Ovelman C, Zupancic JAF. Systemic corticosteroids for the prevention of bronchopulmonary dysplasia, a network meta-analysis. *Cochrane Database of Systematic Reviews* 2020;9:CD013730.
- Lim W, Ridge CA, Nicholson AG, *et al.* The 8<sup>th</sup> lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. *Quant Imaging Med Surg* 2018;8:709–18.
- Covidence systematic review software, V.H.I., Melbourne, Australia.
- Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
- Review Manager (RevMan) [Computer program]. Version 5.4, T.C.C. 2020.
- R Core Team. *R: a language and environment for statistical computing.* R foundation for statistical computing, V, 2020. <https://www.R-project.org/>
- Sterne JAC, Savović J, Page MJ, *et al.* Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366: :14898.
- Higgins J, Thomas J, Chandler J. *Cochrane Handbook for systematic reviews of interventions*, 2008.
- Sterne JA, Hernán MA, Reeves BC, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
- Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015;15:58.
- Higgins JPT, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 2019;22:153–60.
- Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Stat Med* 2003;22:2693–710.
- Sidik K, Jonkman JN. A simple confidence interval for meta-analysis. *Stat Med* 2002;21:3153–9.
- Veroniki A *et al.* “Recommendations for Quantifying the Uncertainty in the Summary Intervention Effect and Estimating the between-Study Heterogeneity Variance in Random-Effects Meta-Analysis.”. *Cochrane Database of Systematic Reviews* 2015:25–7.
- König J, Krahn U, Binder H. Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. *Stat Med* 2013;32:5414–29.



- 38 White IR, Barrett JK, Jackson D, *et al.* Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012;3:111–25.
- 39 et al Gerta Rücker UK, König J, Efthimiou O. netmeta: network meta-analysis using Frequentist methods. R package version 1.3-0, 2021. Available: <https://CRAN.R-project.org/package=netmeta>
- 40 Salanti G, Marinho V, Higgins JPT. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *J Clin Epidemiol* 2009;62:857–64.
- 41 Fujii T, Belletti A, Carr A, *et al.* Vitamin C therapy for patients with sepsis or septic shock: a protocol for a systematic review and a network meta-analysis. *BMJ Open* 2019;9:e033458.
- 42 Furukawa TA, Barbui C, Cipriani A, *et al.* Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol* 2006;59:7–10.
- 43 Sterne JAC, Sutton AJ, Ioannidis JPA, *et al.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
- 44 Chaimani A, Higgins JPT, Mavridis D, *et al.* Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;8:e76654.
- 45 Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Res Synth Methods* 2012;3:161–76.
- 46 Mavridis D, Efthimiou O, Leucht S, *et al.* Publication bias and small-study effects magnified effectiveness of antipsychotics but their relative ranking remained invariant. *J Clin Epidemiol* 2016;69:161–9.
- 47 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, *et al.* Cinema: an approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020;17:e1003082.
- 48 Papakonstantinou T, Nikolakopoulou A, Higgins JPT, *et al.* Cinema: software for semiautomated assessment of the confidence in the results of network meta-analysis. *Campbell Syst Rev* 2020;16:e1080.
- 49 Cinema. Available: <https://cinema.ispm.unibe.ch>